COMPARISON OF EFFECT OF ISOFLURANE AND SEVOFLURANE ON LEFT VENTRICULAR DIASTOLIC FUNCTION, IN PATIENTS WITH ISCHEMIC HEART DISEASE UNDERGOING CORONARY ARTERY BYPASS GRAFTING USING CARDIOPULMONARY BYPASS: AN INTRAOPERATIVE TRANSESOPHAGEAL ECHOCARDIOGRAPHIC STUDY

Thesis submitted for the partial fulfillment for the requirement of The degree of

DM (Cardiothoracic and Vascular Anesthesiology)
of
S.C.T.I.M.S.T

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DECLARATION

I hereby declare that this thesis entitled, "**Comparison of effect of isoflurane and sevoflurane on left ventricular diastolic function, in patients with ischemic heart disease undergoing coronary artery bypass grafting using cardiopulmonary bypass: An intraoperative transesophageal echocardiographic study**" has been prepared by me under the capable supervision and guidance of Prof. Shrinivas Gadhinglajkar , Prof. Rupa Sreedhar, Division of Cardiothoracic and Vascular Anesthesiology, Department of Anesthesiology, and Prof. Jaya Kumar. K, Professor and Head, Department of Cardiothoracic and Vascular Surgery, at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

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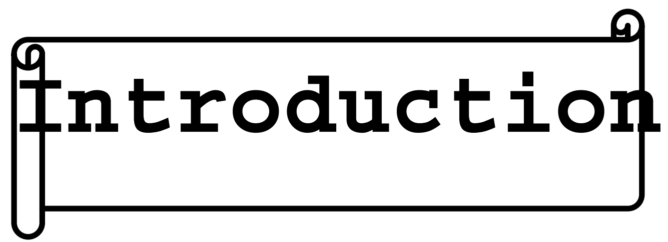
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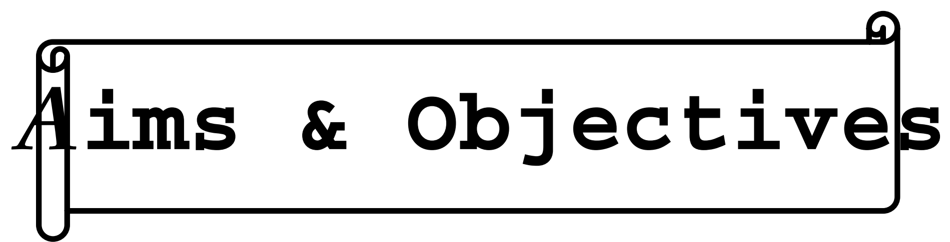
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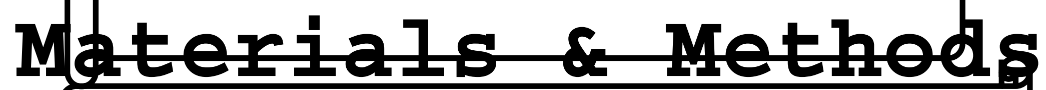

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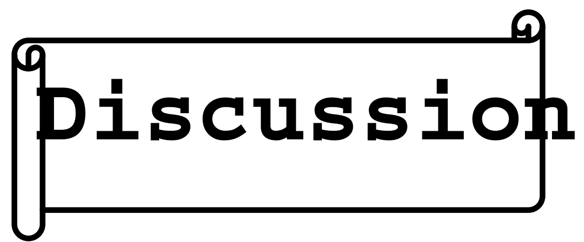
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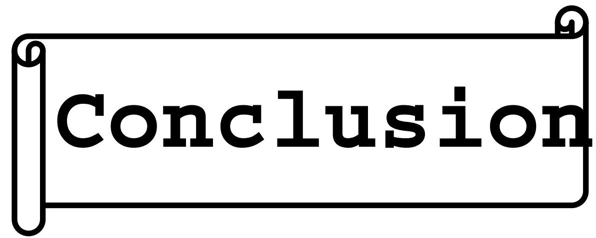
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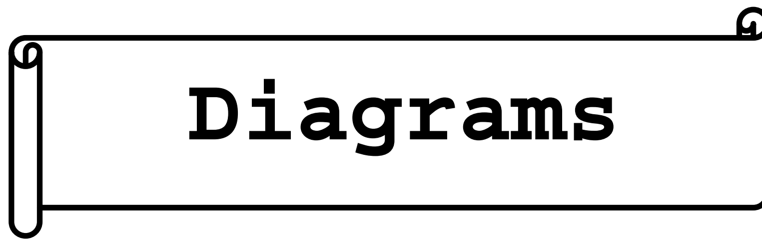
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INTRODUCTION

Diastolic dysfunction has been increasingly recognized as an important cause of congestive heart failure (CHF) and resultant mortality and morbidity. About 50% patients with CHF have 'diastolic heart failure' in spite of a normal systolic function with preserved ejection fraction' [1]. Patients with ischemic heart disease (IHD), hypertrophic cardiomyopathy and systemic hypertension may have signs of CHF due to diastolic dysfunction in the absence of, or, preceding impairment of systolic function. Diastolic dysfunction is highly predictive of adverse events after myocardial infarction [2].

In patients undergoing cardiac surgery, a strong association has been found between the perioperative diastolic dysfunction with the preoperative co-morbid factors like myocardial infarction (MI), regional wall motion abnormalities (RWMA), post-operative inotrope requirements and difficulty in weaning from cardiopulmonary bypass (CPB) [3]. Association between the preoperative asymptomatic ventricular dysfunction (systolic and diastolic) and increased postoperative incidence of CHF, prolonged hospital stay [4], 30 day mortality and long term mortality and morbidity [5] has also been reported in vascular surgical patients.

The widely used volatile anesthetic agents, Isoflurane and Sevoflurane, are considered indispensable components of balanced anesthesia technique. Their cardiovascular effects on myocardial systolic function, cardiac electrophysiology, coronary vasoregulation, systemic and pulmonary vasculature, baroreceptor reflex and anesthetic preconditioning

are well described in the literature [6]. However their effects on left ventricular (LV) diastolic function have not been precisely defined. This is because the indices of diastolic function could not be measured reliably and non-invasively in the past. The diastolic function could be evaluated using invasive methods alone and that too in the experimental design and not in patients. With the advent of echocardiography with Doppler, measurement of diastolic function became feasible in clinical settings. Transesophageal Echocardiography (TEE) has proved to be an excellent tool to investigate and diagnose perioperative diastolic dysfunction, which may influence the anesthetic management and post-operative outcome indirectly. The effects of Isoflurane and Sevoflurane on LV diastolic function have been evaluated in numerous animal experiments and a few human trials, although with conflicting results. Differences in study population (animals versus humans), medication doses (higher experimental doses versus lower clinically applied doses) and methodology (invasive pressure measurements versus echocardiography with Doppler techniques) may account for these contradictory results [7]. Some of the animal studies that employed invasive methods to quantify the diastolic function concluded that volatile anesthetics directly impair LV diastolic relaxation and ventricular filling and indirectly affect diastolic function by depressing LV systolic function [8]. Also, results in patients with normal diastolic function were different when compared with patients with pre-existing diastolic dysfunction. Contrary to the results of animal studies, the volatile anesthetics Halothane and Sevoflurane did not cause clinically relevant impairment of diastolic function in patients with normal diastolic function [9]. On the other hand, in patients with pre-existing diastolic dysfunction, Sevoflurane improved LV relaxation parameters [10].

This study was designed to quantify and compare the effects of Isoflurane and Sevoflurane on left ventricular diastolic function, which was assessed using TEE examination before the establishment of CPB in patients with IHD operated for CABG.

AIMS AND OBJECTIVES

We hypothesize that both Isoflurane and Sevoflurane adversely alter the left ventricular diastolic function.

The objectives of our study were:

1. To evaluate whether the Isoflurane and Sevoflurane adversely affect echocardiographic parameters of LV diastolic function.
2. To compare the effects of Isoflurane and Sevoflurane on echocardiographic LV diastolic parameters.

PATHOPYSIOLOGY

Diastole is physiologically defined as the period of ventricular filling, which occurs during the phase of the cardiac cycle that extends from the closure of aortic valve to the closure of mitral valve. At a cellular level, diastole involves consumption of ATP, unlinking of actin and myosin cross-bridges, followed by reduction of sarcoplasmic calcium concentration and its separation from troponin.

Diastole is divided into four phases [11]:

1) Isovolumic relaxation:

The LV pressure decreases as the LV relaxes actively by an energy consuming process. The aortic valve closes when the LV pressure falls below aortic pressure.

2) Early ventricular filling:

The LV continues to relax actively and the LV pressure falls below left atrial (LA) pressure, resulting in mitral valve (MV) opening, and the early ventricular filling phase begins. Blood now enters the LV down the LA-LV pressure gradient.

LV relaxation is affected by:

- Load: Increased afterload delays myocardial relaxation
- Inactivation: Myocardial inactivation involves all processes leading to cytosolic calcium extrusion and cross-bridge detachment.
- Asynchrony: Asynchronous relaxation in different myocardial segments leads to global delayed relaxation and elevated filling pressures.

Degree of Early ventricular filling is determined by:

- LA-LV pressure gradient
- Effectiveness of LV suction force.

The LV end diastolic properties which affect LV filling are:

Intrinsic factors -

Myocardial stiffness

Myocardial tone

Chamber geometry

Wall thickness

Extrinsic factors -

Pericardial restraint

Ventricular interaction.

3) Diastasis:

During this phase, equilibrium is reached between LA and LV pressures and flow is usually absent

4) Late ventricular filling

LA contraction contributes to late ventricular filling phase, and normally contributes to 30% of LV filling.

QUANTIFICATION OF DIASTOLIC FUNCTION

[A] Invasive methods [12]

Indices of diastolic function can be measured with the help of invasively implanted, high fidelity pressure transducers.

1. Peak rate of LV pressure decrease (*dP/dt* $_{min}$):

It is used to quantify Isovolumic relaxation during early phase of diastole.

2. Time constant ( )

LV pressure decline follows an exponential time course between aortic valve closure and mitral valve opening, which is known as the Time Constant ( ). It is derived as follows:

$$P(t) = P_0 e^{-t/\ } + P_a \quad ,$$

P (t) = Time dependent LV pressure

P_0 = LV pressure at end- systole

e = natural exponent

t= time (in msec) after end systole

P_a = true asymptote to which pressure declines

Time constant increases during disease processes like myocardial ischemia, pressure overload hypertrophy, HCM, negative inotropic agents including volatile anesthetics. Reduction in time constant is seen during tachycardia, sympathetic nervous system

activation and positive inotropic agents. Interpretations of time constant alterations require simultaneous description of loading conditions. Time constant is directly related to preload and afterload. Afterload directly affects duration, rate and extent of LV relaxation. Thus, afterload reduction not only enhances LV systolic function, but also facilitates LV relaxation.

3. Indices of LV filling

The first derivative of LV volume signal with respect to time (*dV/ dt*) can be calculated from invasive measurement of continuous LV volume. The (*dV/ dt*) signal is analogous to the transmitral blood flow and annular velocity signals obtained by Pulse wave (PW) and Tissue Doppler (TD) echocardiography, respectively.

4. Passive Elastic Compliance

It is derived from the 'end diastolic pressure – volume relationship' (EDPVR) obtained from a series of differentially loaded LV pressure – volume loops. The EDPVR is calculated as follows:

$$P_{ed} = A\, e^{KVed} + B$$

Where,

P_{ed} = End diastolic pressure.

Ved = End – diastolic volume

A & B = Curve fitting constants

K = Modulus of chamber stiffness (End- diastolic elastance)

e = natural exponent.

K is increased in pressure overload hypertophy,indicating that LV has become less compliant. LV geometry, mass and wall thickness also influence K.

5. Stress – Strain relationship and Viscoelastic properties.

They are material properties of the myocardium, independent of size, geometry and external forces. As per Hooke's Law, the myocardium will develop a resistive force (σ = Stress) as muscle length (ε = Strain) increases during LV filling. Viscoelasticity is observed when the forces resisting further alterations in length are dependent on the magnitude of change in length and rate at which the change occurs. Their relationship is given by the following:

$$\sigma = \alpha (e_{\beta\varepsilon} - 1) + \eta (d\varepsilon / dt)$$

Where

α = Coefficient of gain

β = Modulus of myocardial stiffness

η = Viscoelastic constant

($d\varepsilon / dt$) = rate of change of strain.

[B] Non – invasive methods (Echocardiography with Doppler)[13].

Echocardiography with Doppler utilizes four methods to determine diastolic function.

(1) Transmitral blood flow velocity:

Transmitral blood flow (TMBF) velocity is measured in midesophageal 4 chamber (ME4C) view by placing a 1-3 mm^3 Pulse wave Doppler (PWD) sample volume between the tips of the MV leaflets during diastole. The TMBF consists of two peaks corresponding to early LV filling and late LV filling due to LA systole (E and A waves , respectively). The peak E and A velocity, E/A ratio, E wave deceleration time (DT) and A wave duration (Adur) are measured. The TMBF velocity patterns are affected by loading conditions (preload and afterload), heart rate, abnormal atrio-ventricular conduction, atrial arrhythmias and mitral valve disorders.

(2) Pulmonary venous blood flow velocity:

Pulmonary venous (PV) blood flow velocity is interrogated by placing a 1-3 mm^3 Pulse wave Doppler (PWD) sample volume 0.5 - 1 cm into right or left upper pulmonary vein to obtain a crisp velocity profile. PV flow velocity is highly dependent on loading conditions of LA and LV, heart rate, and LA function.

Typical PV flow pattern consists of the following waves:

Systolic (S) wave: the first positive wave that occurs during LV systole and isovolumic relaxation (IVR) phase when MV is closed. It displays biphasic morphology (S_1 and S_2). S_1 is caused by LA relaxation and resultant forward blood flow from PVs to LA.

Subsequently mitral annular descent during LV systole causes piston like effect to draw additional blood into LA. S_2 is produced by transmission of RV systolic pressure pulse through the pulmonary circulation.

Diastolic (D) wave: it is the second positive wave that occurs that occurs after MV opening and rapid fall in LA pressure that accompanies early LV filling. The D wave velocity is dependent on LV compliance and the extent of early LV filling. Thus, delayed relaxation or reduced LV compliance attenuate D wave velocity.

Atrial reversal (Ar) velocity: it is a small negative deflection that indicates retrograde flow from LA into the PVs due to LA contraction. It is affected by LA preload and contractile state and LV pressure during late diastole

(3) Tissue Doppler Imaging (TDI) :

Mitral annular tissue Doppler waveforms are acquired from ME4C view using low velocity (10 – 15 cm/sec) PWD echocardiography. The TDI waveforms show peak velocity associated with early LV filling (e') and LA systole (a'). The e'/a' ratio denotes their relative contributions to LV filling. The ratio of TMBF E to TDI e' (E/e') has been shown to be a reliable estimate of LV filling pressures. e' is affected by rate and extent of LV isovolumic relaxation, LV systolic function and LV preload. However, e' is less affected by LV preload than TMBF E velocity, especially when LV relaxation is delayed. a' is affected by LA contractile function and LV diastolic pressure. Usefulness of TDI is limited by mitral annular calcification, prosthetic MV or MV rings or MV pathologies.

(4) Colour M - mode propagation velocity (Vp)

Colour M - mode propagation velocity is acquired by placing the M – mode scan line into the centre of the LV inflow aligned from MV to the LV apex. The Vp is given by the slope of the first aliasing velocity. It quantifies the rapidity of movement of blood from MV to apex. The extent of LV relaxation and elastic recoil are the primary determinants of Vp. However, alterations in chamber geometry, contractile dyssynchrony, and blood flow vortex formation may limit the use of Vp as a quantitative index.

GRADING OF DIASTOLIC DYSFUNCTION

Diastolic function can be graded into four stages[14]:

(1) Normal pattern

Normal diastolic function is characterized by

- E/A > 1
- DT < 220ms
- IVRT <100ms
- S/D > 1
- PV Ar velocity < 35 cm/sec
- Vp > 45 cm/sec
- e’ > 8 cm/sec

(2) Impaired relaxation (Grade I)

In a typical impaired relaxation pattern, which is considered the initial stage of diastolic dysfunction, there is:

- E/A ratio <1
- DT > 220 ms
- IVRT > 100 ms
- S/D ratio remains > 1
- PV Ar < 35 cm/s
- Vp < 45 cm/s,
- e’ < 8cm/s

(3) Pseudonormalization (Grade II),

Because of impaired filling during early diastole, blood backs up in the LA and leads to an increase of the LA pressure. The LA pressure, not ventricular relaxation, is the driving force for early LV filling. Because it resembles the normal pattern, it is called a “pseudonormal” pattern. Grade II diastolic dysfunction represents impaired myocardial relaxation with mild to moderate elevation of LV filling pressures.

In such patients with moderate diastolic dysfunction (Grade II),

- E/A ratio = 1 – 2 and decreases by > 50% during the Valsalva maneuver,
- DT = 150 – 200 ms
- IVRT = 60 – 100 ms
- S/D ratio < 1
- PV Ar > 35 cm/s

- Vp < 45 cm/s
- e’ < 8 cm/s
- Ar velocity > 30cm/s and
- S/D ratio < 1.
- LVEDP is increased and is recognized by Ar - A duration > 30 ms.

(4) Restrictive filling (Grade III)

Persistence of relaxation abnormalities due to continued myocardial dysfunction causes LV remodeling and leads to reduced LV compliance, which manifests itself as an increase of LVEDP and an increase in LA pressure. The increased LA pressure overcomes the resistance to LV early filling because of impaired relaxation, and results in increased filling during early diastole and rapid equalization of pressure between the LA and LV because of reduced compliance characterized by an increased E velocity and shortened DT. As a result, there is limited filling during atrial contraction because of decreased LV With severe diastolic dysfunction (grade III), restrictive LV filling occurs with an

- E/A ratio > 2,
- DT < 150 ms,
- IVRT < 60 ms,
- S/D ratio < 1
- Vp < 45 cm/s
- e’ < 8 cm/s.

REVIEW OF LITERATURE

The effect of volatile anesthetic agents on LV diastolic function has been investigated in numerous animal studies and in vitro experiments with myocardial tissue. The human research is limited to a few publications alone. But, in a recent review article, Matyal R et al [15] have stated that the effect of anesthetic drugs on LV relaxation is not clear. Different studies conducted so far have been inconclusive since many of them yielded conflicting results. Differences in study population (animals versus humans), medication doses (higher experimental doses versus lower clinically applied doses), and methodology (Doppler versus invasive pressure measurements) could possibly explain these contradictory results. However these studies have contributed enormously to our knowledge regarding effects of the volatile anesthetic agents on diastolic function. Hence it is necessary to review them systematically.

[A] Animal Studies:

Doyle et al [16] studied the effects of graded concentrations of Halothane on coronary blood flow (CBF), *dP/dt* and time constant of relaxation in 6 dogs undergoing open chest surgery with invasive monitoring. Global and regional left ventricular functions were also measured. Halothane caused dose-dependent depression of contractility, regional shortening, and cardiac output. Halothane also caused significant increases in the time constant of relaxation and decreased and delayed the nadir of peak negative left ventricular *dP/dt*. Dose-dependent reductions of CBF were noted. Percentage CBF during isovolumic relaxation was significantly reduced and showed a strong inverse correlation

with time constant of relaxation. Halothane appears to interfere with the inactivation process of the heart; this in turn may impede the early rise in CBF during isovolumic relaxation.

Humphrey LS et al [17] studied the effects of halothane (0.5, 1.0, and 1.5%; n = 10), enflurane (1.0, 2.0, and 3.0%; n = 8), and isoflurane (0.75, 1.5, and 2.25%; n = 8) on isovolumic relaxation in open-chest swine. The time constant for isovolumic left ventricular pressure decline, T, was determined at each anesthetic concentration at the intrinsic heart rate and during atrial pacing to 150 beats per min. The effect of increased left ventricular afterload on T was investigated by partial occlusion of the thoracic aorta to raise the left ventricular systolic pressure to baseline in the presence of volatile anesthetics, and 20% above baseline in the absence of volatile anesthetics. Heart rate and left ventricular systolic pressure decreased substantially with all three anesthetics, whereas left ventricular end-diastolic pressure increased (by 3-4 mmHg). Relaxation time constants increased with all three anesthetics at the intrinsic heart rate; when the heart rate was controlled by pacing, T increased in the halothane and enflurane, but not in the isoflurane, experiments. T was significantly prolonged (by 30-100%) by partial aortic occlusion in the presence of anesthetic, but not in the control measurements. T did not change significantly in the isoflurane experiments when atrial pacing was employed with partial aortic occlusion. They concluded that the volatile anesthetics, particularly halothane, seem to impair the relaxation process of the left ventricle; further investigation of the mechanisms of this interference, such as anesthetic effects on intracellular calcium movement and total left ventricular load, is warranted.

Pagel et al conducted a large series of animal experiments that described the effects of volatile anesthetics on invasively derived indices of LV systolic and diastolic function.

Pagel et al[18], 1991, studied the effects of the new volatile anesthetic desflurane on three indices of left ventricular diastolic function and compared to those produced by equianesthetic concentrations of isoflurane and halothane. Since autonomic nervous system function may significantly influence hemodynamic actions of anesthetics in vivo, experiments were performed in the presence of pharmacologic blockade of the autonomic nervous system. About 23 experiments were performed using 11 dogs instrumented for measurement of aortic and left ventricular pressure, rate of increase of left ventricular pressure (*dP/dt*), subendocardial segment length, and cardiac output. Systemic hemodynamics was recorded in the conscious state and after 30 min equilibration at 1.0 and 1.5 MAC desflurane, isoflurane, or halothane. Ventricular relaxation was described using invasively derived time constants of isovolumetric relaxation. Chamber and myocardial stiffness, and the viscoelastic properties of the ventricle were also described. Desflurane produced a significant and dose-dependent increase in isovolumetric relaxation time. Similar degrees of prolongation of isovolumetric relaxation were produced by isoflurane and halothane. Halothane also caused an increase in regional passive chamber stiffness indicating a decrease in ventricular compliance. No changes in chamber stiffness were observed with desflurane or isoflurane. In addition, no significant changes in myocardial stress-strain relationships were observed with any anesthetic. The results indicated that desflurane, isoflurane, and halothane produce equivalent degrees of

prolongation of isovolumetric relaxation. Halothane also caused a decrease in compliance during passive filling as evaluated by chamber stiffness, but no change in compliance was observed at end diastole as assessed by stress-strain relationships.

Pagel et al [19], 1993, investigated and compared the direct effects of extra cellular Ca^{2+} on left ventricular systolic and diastolic function in conscious and anesthetized dogs. 27 experiments were conducted using nine dogs chronically instrumented for measurement of aortic and left ventricular pressure, left ventricular dP/dt, subendocardial segment length, and cardiac output. Myocardial contractility was evaluated using the preload recruitable stroke work relationship slope (Mw). Diastolic function was assessed using a time constant of isovolumic relaxation, a regional chamber stiffness constant, and maximum segment lengthening velocity during rapid ventricular filling (*dL/dt* E) and atrial systole (*dL/dt* A). On 3 separate days, a CaCl2 infusion at 1.25, 2.5, or 5 mg/kg/min was administered. Hemodynamics and ventricular pressure-length loops were recorded after a 20-min equilibration at each dose in the conscious state or during halothane or isoflurane anesthesia. In conscious dogs, CaCl2 produced a significant ($P < .05$) and dose-dependent increase in contractility as evaluated by Mw. In the presence of halothane anesthesia, CaCl2 increased contractility, enhanced isovolumic relaxation, improved rapid ventricular filling and reduced regional chamber stiffness. Similar findings were observed when CaCl2 was administered to dogs anesthetized with isoflurane. The results showed that although CaCl2 produced positive inotropic effects in both the conscious and anesthetized states, CaCl2 did not alter diastolic function in conscious dogs. In contrast, CaCl2 reversed halothane- and isoflurane-induced negative lusitropic actions. The

authors concluded that improvement of left ventricular performance by CaCl2 during volatile anesthesia may be related to actions in diastole as well as systole.

Harkin CP, Pagel et al [20], 1994, studied the systemic and coronary hemodynamic, inotropic, and lusitropic actions of sevoflurane in chronically instrumented dogs in the presence and absence of autonomic nervous system (ANS) reflexes. Eighteen experiments were performed in nine dogs chronically instrumented for measurement of aortic and left ventricular pressure, rate of change of left ventricular pressure, subendocardial segment length, diastolic coronary blood flow velocity, and cardiac output. The preload recruitable stroke work slope was used to assess myocardial contractility. Diastolic function was evaluated by a time constant of isovolumic relaxation, maximum segment lengthening velocity during rapid ventricular filling, and a regional chamber stiffness constant. Dogs were assigned to receive sevoflurane with or without pharmacologic blockade of the ANS in a random fashion. On separate experimental days, systemic and coronary hemodynamics and left ventricular pressure--segment length diagrams and waveforms were recorded in the conscious state and during sevoflurane anesthesia (1.0, 1.25, 1.5, and 1.75 MAC).

In dogs with intact ANS reflexes, sevoflurane caused significant ($P < 0.05$) increases in heart rate and dose-related decreases in mean arterial pressure, left ventricular systolic pressure, cardiac output, diastolic coronary vascular resistance and myocardial contractility. Sevoflurane prolonged isovolumic relaxation (time constant of isovolumic relaxation) and decreased rapid ventricular filling (maximum segment lengthening velocity) without affecting regional chamber stiffness. Sevoflurane caused similar

alterations in functional indices of left ventricular systolic and diastolic performance in autonomically blocked dogs. The authors thus concluded that Sevoflurane caused direct negative inotropic and lusitropic effects in chronically instrumented dogs with and without ANS blockade.

Pagel et al [21], 1995, examined the regional systolic and diastolic mechanical responses to brief left anterior descending coronary artery (LAD) occlusion in the central ischemic zone and in remote normal myocardium in the conscious state and during desflurane and isoflurane anesthesia. In conscious dogs, LAD occlusion abolished regional stroke work, increased chamber stiffness and decreased the rate of early ventricular filling in the ischemic zone. Conversely, there was increased contractility, rapid filling rate and chamber stiffness in the normal region. Increases in tau were also observed in the conscious state during the period of myocardial ischemia. . Desflurane and isoflurane increased tau and decreased the slope and maximum segment lengthening velocity in a dose-related manner. . Myocardial contractility and rapid filling rate were enhanced in the nonischemic region during LAD occlusion in the presence of desflurane and isoflurane. In contrast to the findings in the conscious state, ischemia-induced increases in tau and chamber stiffness in the ischemic and normal zones were attenuated during anesthesia induced by desflurane and isoflurane. The results indicate that increases in contractility of remote myocardium during brief regional ischemia were preserved in the presence of desflurane and isoflurane anesthesia. In addition, desflurane and isoflurane blunted ischemia-induced increases in tau and regional chamber stiffness in both the ischemic and nonischemic zones. The authors concluded that the volatile anesthetics may exert

important beneficial actions on left ventricular mechanics in the presence of severe abnormalities in systolic and diastolic function during ischemia.

Yamada T et al [22] studied the effects of sevoflurane, isoflurane, enflurane, and halothane on left ventricular diastolic performance in dogs. Thirty-five mongrel dogs were randomly assigned to receive sevoflurane, isoflurane, enflurane, or halothane. Left ventricular pressure waveforms, phonocardiograms, and echocardiograms were recorded after administering the anesthetics at concentrations of 0% (control), 1%, 2%, and 3%. No change in the time constant or in chamber stiffness was observed at any concentration of sevoflurane or isoflurane. However, 3% enflurane and halothane produced a significant increase in the time constant and in chamber stiffness. Rapid filling rate as well as atrial filling rate decreased significantly with all the volatile anesthetics, especially with enflurane and halothane. The authors concluded that sevoflurane and isoflurane did not alter ventricular relaxation or chamber stiffness, but did affect diastolic function as manifested by their alteration of filling rates. With the administration of the volatile anesthetics, the rapid filling rate decreased with the deterioration of diastolic function; in addition, atrial filling rates decreased and did not compensate for the reduction in early ventricular filling.

Graham et al [23] hypothesized that isoflurane and halothane may have even greater effects on diastolic function in the newborn, as the newborn heart has increased passive stiffness and altered calcium handling relative to the adult. They compared Isoflurane and Halothane at three clinically relevant concentrations (0.5, 1.0 and 1.5 MAC) with respect to both systolic and diastolic function in sixteen newborn pigs. . Systolic function was

assessed by peak positive *dP/dt (dP/dTmax)* and the slope of the end-systolic pressure-dimension (ESP-D) relationship. Diastolic relaxation was given by peak negative dP/dT (-dP/dTmax) and the time constant for ventricular relaxation (tau). Left ventricular stiffness was calculated from the slope of the end-diastolic pressure-dimension (EDP-D) relationship. They observed that systolic function was depressed at all anaesthetic concentrations. Diastolic function was affected only at higher MAC anesthesia. Control tau increased with 1.5 MAC isoflurane and halothane, while EDP-D slope was increased and the -dP/dTmax decreased at both 1 and 1.5 MAC anesthesia. They concluded that the combined systolic and diastolic effects help to explain the increased sensitivity of the newborn myocardium to volatile anesthetics.

Hanouz JL et al [24] studied the effects of equianesthetic concentrations (0.5, 1, 1.5, 2 and 2.5 MAC) of sevoflurane, isoflurane and halothane on inotropic and lusitropic variables, and post-rest potentiation in rat left ventricular papillary muscles in vitro. Post-rest potentiation of isometric force is a method of studying the function of the sarcoplasmic reticulum in vitro in a biochemically intact preparation. Sevoflurane and isoflurane caused comparable concentration-dependent negative inotropic effects which were significantly lower than those induced by halothane ($P < 0.05$). Sevoflurane and isoflurane did not modify lusitropic variables under low or high load, whereas halothane showed a negative lusitropic effect at high concentrations. Halothane suppressed post-rest potentiation, whereas isoflurane and sevoflurane did not. Thus in rat myocardium, sevoflurane and isoflurane caused comparable negative inotropic effects, had no significant lusitropic effects and did not alter post-rest potentiation, suggesting that they did not significantly modify the functions of the sarcoplasmic reticulum.

Summary of results of animal studies:

Volatile anesthetics produce dose-dependent direct negative inotropic effects as demonstrated by reductions in the slope of the LV end-systolic pressure-dimension or -volume relation and preload recruitable stroke work. These actions are accompanied by delays in LV isovolumic relaxation (e.g. increases in τ) and reductions in rate and extent of early LV filling. The rapid filling rate decreased with the deterioration of diastolic function; in addition, atrial filling rates decreased and did not compensate for the reduction in early ventricular filling. However, volatile anesthetics did not affect LV end-diastolic pressure-dimension relations, indicating that these drugs do not alter the passive mechanical behavior of LV myocardium. The volatile anesthetic-induced alterations in LV diastolic function occur as a consequence of depression of myocardial contractility and not because of a direct negative lusitropic effect. This conclusion was supported by the results of studies examining the influence of volatile agents in isolated cardiac muscle preparations in vitro. Volatile anesthetics do not significantly modify the functions of the sarcoplasmic reticulum. It was also observed that unlike systolic function, diastolic function was affected only at higher MAC of anesthetic agents. Desflurane, isoflurane, sevoflurane and halothane produce equivalent degrees of prolongation of isovolumetric relaxation. Halothane and enflurane at higher concentrations also caused a decrease in compliance during passive filling as evaluated by chamber stiffness. The alterations of intracellular calcium ($Ca2+$) homeostasis within the myocardial cells may be involved in the mechanism of effects of volatile anesthetics on diastolic function.

[B] Human studies:

Compared to the large number of animal experiments, human studies on the effects of volatile anesthetics on LV diastolic function are very few.

Houltz et al [25] investigated the effects of halothane and isoflurane, when used to control the stress response to sternotomy in 33 patients with coronary artery disease (CAD). LV early diastolic relaxation and end-diastolic stiffness were evaluated from mitral Doppler flow profiles, transesophageal two-dimensional echocardiography, and central hemodynamic measurements. Measurements were performed a) after induction of anesthesia, b) after volume loading, c) prior to surgery and d) during surgery, 10 min after introduction of the inhalation anesthetic. The effects of the anesthetics on Doppler indices reflecting early diastolic relaxation, and on the left ventricular end-diastolic pressure-area (LVED P/A) relationship, were studied. When data obtained during surgical stress were compared to the control situation, they found an increase in the LV filling pressures in both groups, while only the isoflurane group showed an increase in heart rate. An increase in end-systolic LV area and decreased fractional area change was present in the halothane group. In both the groups, there was an increase in LV end-diastolic area. The mitral Doppler indices showed decreases of deceleration rate and time of early diastolic filling, indicating an impairment of early diastolic relaxation, in both groups. Isoflurane induced a displacement of the LVED P/A relationship leftwards from the baseline curve. They concluded that both halothane and isoflurane impair early diastolic relaxation in patients with CAD, when used to control intraoperative surgical

stress. In contrast to halothane, isoflurane induced a change in the LVED P/A relationship, suggestive of an increased LVED stiffness.

Oxorn D et al [26] studied the effect of isoflurane on left ventricular diastolic function in ten patients with normal cardiovascular function as assessed by Doppler echocardiography. Doppler measurements of mitral inflow velocities, and pulmonary venous blood flow velocities were measured preoperatively by transthoracic echocardiography (TTE), and intraoperatively by transesophageal echocardiography (TEE) at isoflurane MAC 1 and MAC 1.5. Heart rate and blood pressure were measured concomitantly. The results showed that isoflurane at both doses caused equal decreases in mitral inflow A (atrial systole) velocity (Control 43 ± 12.3 cm/sec vs 31± 6.0 cm/sec at 1 MAC and 31.3 ± 7.9 cm/sec at 1.5 MAC ; $P < 0.01$), the deceleration time of the mitral inflow E (early) velocity (Control 178 ± 31.7 msec versus 127 ± 38.3 msec at 1 MAC and 137 ± 28.4 msec at 1.5 MAC ; $P < 0.01$), and mean blood pressure (control: 91.1 ± 15.4 mmHg versus 76.1 ± 8.8 mmHg at 1 MAC and 71.9 ± 6.2 mmHg at 1.5 MAC ; $P < 0.002$). Isoflurane at both doses caused an equal increase in the E/A ratio (control: 1.5 ± 0.57 vs 2.0 ± 0.6 at 1 MAC and 2.2 ± 0.78 at 1.5 MAC; $P < 0.01$). No changes in mitral inflow E or pulmonary venous velocities were seen.

The findings in the study were 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 were consistent with increased left ventricular restriction, there was a lack of change in the mitral inflow E velocity, pulmonary venous AR velocity, and pulmonary venous S/D ratio. The most likely explanation for the

observations was probably the effects of isoflurane on afterload, contractility, and atrial systolic function. Left ventricular systolic impairment would have caused 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 probably resulted 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 suggested that there were no differences in left atrial pressure, and thus, no change in left ventricular preload. The decreased mitral A velocity in their study was therefore most likely the result of a negative inotropic effect of isoflurane on atrial systolic function.

The authors concluded that the changes in Doppler velocities of mitral inflow and pulmonary venous flow with isoflurane were not consistent with prolonged left ventricular relaxation nor increased myocardial restriction, but were more likely the result of alterations in left ventricular loading conditions and atrial systolic function. They speculated that increasing the dose further would have led to more profound Doppler changes; the haemodynamic consequences, however, would have probably been intolerable. They mentioned that apart from the small, under-powered sample size, the major limitation of the study was the comparison of Doppler velocity measurements between TI'E and TEE; as they were uncertain that the two techniques yield comparable results. They opined that future studies will be required to examine the effects of isoflurane on Doppler derived indices of left ventricular filling, especially in patients with preexisting abnormalities of left ventricular diastolic function.

Neuhäuser C et al [27] performed a prospective, experimental study.in twenty-five patients with diastolic dysfunction due to concentric hypertrophy and ischemic heart disease undergoing elective coronary artery bypass graft surgery (CABG). They investigated

whether isoflurane exacerbates diastolic dysfunction in such patients with preexisting impaired relaxation. The patients randomly received sufentanil/midazolam anesthesia plus either 0.5 to 1.0 minimum alveolar concentration (MAC) of isoflurane (n - 15) or weight-adjusted boli of urapidil (n - 10) during preparation of the internal mammary artery. Changes in hemodynamic parameters and echocardiographic diastolic indices before and after drug administration were compared.

Hemodynamic changes measured by invasive arterial and pulmonary arterial pressures were comparable between isoflurane and urapidil. Both interventions led to a marked reduction in afterload that was accompanied by a significant increase in thermodilution cardiac output and stroke volume. Transesophageal echocardiographic relaxation indices were also comparable between groups. Transmitral and tissue Doppler E waves increased significantly, leading to larger E/A and Em/Am ratios; whereas the deceleration time (DT) and the isovolumetric relaxation time (IVRT) decreased significantly.

The main result of this study was that clinical concentrations of isoflurane, a known negative lusitropic agent, did not further impair relaxation in patients with preexisting diastolic dysfunction because of LV hypertrophy and ischemic heart disease. In contrast, an improvement in hemodynamics and a “normalization” of Doppler-echocardiographic filling indices were observed after isoflurane administration. This “normalization” occurred while filling pressures remained within a normal range. It therefore can be

distinguished from pseudonormalization, which is seen when filling pressures are pathologically elevated.

The decrease in IVRT as well as the increase in E and Em suggested improved relaxation during the study. However, unloading the heart also decreases IVRT. As aortic pressure falls (with constant LAP), the aortic valve closes later, and IVRT is reduced independent of relaxation. DT depends on chamber compliance in early diastole. During cardiac surgery, a decrease of DT with 1.0 MAC isoflurane has been described and was correlated to an upward shift in an end-diastolic pressure-volume curve. The relative constancy of the diastolic pressure-volume relation in humans after acute interventions (including volatile agents) has led to the strong suspicion that LV compliance is rarely changed acutely. Changes in loading conditions as well as the inotropic state are more likely to cause the LV to operate on a steeper region of the pressure-volume curve, rather than direct alterations of the intrinsic viscoelastic properties of the myocardium. Incorrect interpretation of diastolic indices may suggest diastolic dysfunction when it is not present, or may lead to the assumption that a pharmacologic intervention successfully corrected the abnormality when it merely changed LV loading conditions.

The authors suggested that the main part of the observed diastolic effect was caused by a reduction in afterload. Loads applied early in the contraction generally prolong the rate of early filling. During contraction, calcium is available to the contractile proteins, more cross bridges are recruited, and systole is prolonged. Furthermore, LV hypertrophy is accompanied by delayed removal of calcium from the microfilaments and the intracellular space during diastole because of alterations in sarcoplasmic reticulum

calcium pump adenosine triphosphatase (SERCA) and phospholamban. In combination, myocardial relaxation and filling occur later and at a slower rate. Myocardial ischemia may even aggravate the situation since relaxation is a time- and energy-consuming process.

Filipovic M et al [28], in 2005, evaluated the effects of halothane, sevoflurane and propofol on left ventricular diastolic function in humans with normal cardiovascular status during spontaneous and mechanical ventilation. Sixty patients (aged 18–47 yr) who had no history or signs of cardiovascular disease were randomized to receive general anesthesia with halothane, sevoflurane or propofol. Echocardiography (TTE) was performed at baseline and during spontaneous respiration at 1 minimum alveolar concentration (MAC) of the inhalational agents or propofol 4 mg/ ml (step 1), and repeated during positive-pressure ventilation with 1 and 1.5 MAC of the inhalational agents or with propofol 4 and 6 mg /ml by TEE (steps 2A and 2B). Analysis of echocardiographic measurements focused on heart rate corrected isovolumic relaxation time (IVRTc) and early diastolic peak velocity of the lateral mitral annulus (Ea).

The results indicted that IVRTc decreased from baseline to step 1 in the halothane group, remained stable in the sevoflurane group and increased in the propofol group. Ea decreased in the propofol group only. From step 2A to step 2B, IVRTc increased further in the propofol group but remained stable in the other two groups. Ea did not change from step 2A to step 2B. FAC decreased in the sevoflurane and halothane groups but remained unchanged in the propofol group.

Thus, during spontaneous ventilation (step 1), halothane and sevoflurane at 1 MAC had no evidence of impairment of LV relaxation and early filling, as IVRTc and Ea did not change. In contrast, halothane and sevoflurane impaired LV late filling. LV late filling is determined mainly by left atrial systolic function, a parameter that was not measured in this study. Also during IPPV (step 2), they found no evidence for impairment of LV relaxation and LV early filling by halothane or sevoflurane. Reduction in late LV filling with the inhalational agents persisted during IPPV. Also, the difference in LV early filling disappeared during IPPV and Ea was similar in all study groups. They suggested that the negative effect on venous return of anesthesia with muscle paralysis and IPPV may have attenuated the effects of the three agents on early filling. The absence of impairment of diastolic function by inhalational agents contrasted with the clear impairment of systolic function as indicated by the decrease in FAC by halothane and, to a lesser extent, sevoflurane. The stability of IVRTc during impaired LV systolic function further supported the evidence for the lack of impairment of LV relaxation and early filling by the inhalational agents as diastolic function is dependent on systolic function.

In contrast with halothane and sevoflurane, IVRTc increased and Ea decreased significantly during the administration of propofol, indicating some impairment of LV relaxation and early filling. They concluded that halothane and sevoflurane did not influence LV relaxation but propofol caused some impairment. However, the magnitude of impairment by propofol was small and unlikely to cause clinically significant diastolic dysfunction in patients who have no cardiovascular disease.

Filipovic M et al [29], in 2007, investigated the effects of sevoflurane and propofol on left ventricular diastolic function in patients with pre-existing diastolic dysfunction. 23 randomized patients who fulfilled the predefined echocardiographic criterion for diastolic dysfunction received general anesthesia with sevoflurane 1 MAC (n=12) or propofol 4mg/ml (n=11). Echocardiographic examinations were performed at baseline and in anaesthetized patients under spontaneous breathing and under positive pressure ventilation. Analysis focused on peak early diastolic velocity of the mitral annulus (Ea). Spontaneous breathing) allowed for performing anesthesia solely with the one anesthetic and to avoid the effect of IPPV on venous pooling, preload and afterload. During spontaneous breathing, Ea was higher in the sevoflurane than in the propofol group [mean (95% CI) 7.0 (5.9–8.1) vs 5.5 (4.7–6.3) cm/s; $P<0.05$], reflecting an increase of Ea from baseline only in the sevoflurane group ($P<0.01$). During positive pressure ventilation, Ea was similarly low in the sevoflurane and propofol groups [5.3 (4.2–6.3) and 4.4 (3.6–5.2) cm/s, respectively]. It was also noted that sevoflurane impaired systolic atrial and ventricular functions, as indicated by decreases of Sa and Aa. In contrast, these variables were unchanged during propofol anesthesia. They concluded that during spontaneous breathing, early diastolic function improved in the sevoflurane but not in the propofol group. However, during positive pressure ventilation and balanced anesthesia, there was no evidence of different effects caused by the two anesthetics. The findings demonstrated ongoing impairment of diastolic function under balanced anesthesia but did not favor sevoflurane or propofol as an agent that would be advantageous inpatients with pre-existing diastolic dysfunction

Bolliger D et al [30] studied the effects of sevoflurane, desflurane, and isoflurane on early and late left ventricular diastolic function in young healthy adults. Sixty healthy subjects (aged 18–48 yr) undergoing minor procedures under general anesthesia were studied. After randomization for the anesthetic, transthoracic echocardiographic examinations were performed at baseline and under anesthesia with 1 minimum alveolar concentration (MAC) of the volatile anesthetics during spontaneous breathing and intermittent positive pressure ventilation (IPPV). Peak early (Ea) and late (Aa) diastolic velocities of the mitral annulus were studied as the main echocardiographic indicators of diastolic function. They observed that the haemodynamic changes were comparable in all study groups. During anesthesia with 1 MAC under spontaneous breathing, Ea increased with desflurane, was not significantly different with isoflurane, and decreased with sevoflurane. During IPPV, Ea was similar to baseline with desflurane, insignificantly decreased with isoflurane, and decreased with the sevoflurane group. In contrast, Aa was similarly reduced in all groups during spontaneous breathing without further changes during IPPV. They concluded that desflurane and isoflurane, and most likely sevoflurane, have no clinically relevant negative effect on early diastolic relaxation in young subjects without cardiovascular disease. In contrast, volatile anesthetics appear to decrease global atrial function, thereby potentially impairing late diastolic LV filling. They further opined that the findings of this study cannot be directly transferred to patients with pre-existing diastolic dysfunction. Therefore, further studies investigating the effects of volatile anesthetics in this patient population under controlled conditions were warranted.

Summary of results of human studies:

The results of the human studies on the effects of isoflurane on LV diastolic function are not consistent with prolonged left ventricular relaxation nor increased myocardial restriction, but were more likely the result of alterations in left ventricular loading conditions and atrial systolic function. Also, some differences were noted in the effects in patients with normal cardiovascular status and those with pre-existing diastolic dysfunction. .

In patients with normal cardiovascular function, there was a decrease in late ventricular filling A velocity, decreased DT and increased E/A ratio with isoflurane ; but there was no change in early ventricular filling E velocity and pulmonary venous flow patterns. The decreased mitral A velocity was most likely the result of a negative inotropic effect of isoflurane on atrial systolic function. The findings do not indicate impaired left ventricular relaxation, because, although the increased E/A ratio and shortened deceleration time of the mitral inflow E velocity were consistent with increased left ventricular restriction, there was a lack of change in the mitral inflow E velocity, pulmonary venous Ar velocity, and pulmonary venous S/D ratio.

In tissue Doppler studies, isoflurane caused reduced e' velocity during IPPV, while sevoflurane decreased e' both during spontaneous ventilation and IPPV; but this was not considered to be clinically significant. . a' was consistently depressed by all volatile agents indicating a negative inotropic effect of on atrial systolic function. Impairment of systolic atrial function potentially impairs late diastolic LV function.

In patients with pre-existing diastolic dysfunction, E and e' increased, resulting in increased E/A and e'/a' ratio, while DT and IVRT decreased with isoflurane. The

decrease in IVRT as well as the increase in E and e’ suggested improved relaxation or normalization of Doppler-echocardiographic filling indices. This “normalization” occurred while filling pressures remained within normal range and therefore can be distinguished from pseudonormalization, which is seen when filling pressures are pathologically elevated. Similarly, during spontaneous breathing, early diastolic function was noted to improve with sevoflurane in patients with diastolic dysfunction. The effects on loading conditions as well as the inotropic state are more likely to cause the LV to operate on steeper region of the pressure-volume curve and this was the reason for the apparent “normalization”, rather than direct alterations of the intrinsic viscoelastic properties of the myocardium.

MATERIALS AND METHODS

The prospective, randomized and observational study was conducted in a tertiary referral center and a university level hospital. The participants included patients who were operated for elective CABG using cardiopulmonary bypass. Patients belonging to the age of 50-70 years and either gender, and those with triple vessel disease having the preoperative left ventricular ejection fraction (LVEF) >55% were included in the study groups. The exclusion criteria were: esophageal disease, coexisting valvular heart disease, pre-existing Grade II (pseudonormal filling) and Grade III (restrictive filling) diastolic dysfunction, HOCM/other cardiomyopathies, pericardial disease/effusion, severe lung disease, age < 50 years or > 70 years, preoperative atrial fibrillation or other haemodynamically significant arrhythmias, pre-CPB inotropic support requirement, LVEF < 55%, pre-existing severe left ventricular hypertrophy, unwilling to give consent for participation in the study protocol, emergency CABG, and patients with single-vessel or double-vessel coronary artery disease.

50 patients undergoing elective CABG using cardiopulmonary bypass were enrolled in the study. A computer generated randomization protocol was used to allocate them into 2 groups.

25 patients in Group – I received Isoflurane, and

25 patients in Group – II received Sevoflurane.

After the approval of Institutional Ethics Committee and obtaining informed, written consent, 50 patients with IHD who satisfied the inclusion and exclusion criteria were enrolled in the study. All patients were thoroughly examined during pre-anesthetic evaluation and educated regarding study protocol. The preoperative cardiac medications

were continued in the morning of surgery except the ACE inhibitors. The oral hypoglycemic drugs and insulin in diabetics were omitted in the morning of surgery. All of them were premedicated with Inj. morphine 0.1mg/Kg and Inj. glycopyrrolate 0.2mg intramuscularly, 45 mins before surgery. On arrival in the operating room, the pulse oxymetry probe, a 5-lead ECG and BIS electrodes were attached. Intravenous access was obtained and radial arterial canulation was performed under local anesthesia. General anesthesia was induced with intravenous fentanyl 15 micrograms /Kg, midazolam 0.1 mg/Kg and pancuronium 0.15 mg/Kg. Anesthesia was maintained with 1-2 % Sevoflurane in 50% oxygen and air. A triple lumen central venous catheter was inserted in right internal jugular vein. A multiplanar TEE probe (iE 33, Philips Medical Systems, Bothell, WA) was inserted. IV infusion of propofol was started at the dose range of 50 – 100 mcg/kg/min before discontinuation of sevoflurane. The propofol infusion was titrated to maintain the BIS value between 40 to 60. After sternotomy, the sevoflurane administration was discontinued. When the end-tidal sevoflurane concentration declined to zero, the heart was examined using TEE and baseline measurements pertaining to the LV diastolic function were obtained as per the ASA/ SCA guidelines. If the TEE examination revealed any finding that met with the exclusion criteria, and which was not detected during preoperative evaluation, the patient was not considered for the study protocol. The enrolled patients were randomly allocated to receive either 1 MAC (minimum alveolar concentration) of isoflurane or sevoflurane. IV fluids were administered and intermittent boluses of phenylephrine 50 – 100 micrograms were injected to maintain the central venous pressure (CVP) of 6-10 mm Hg and mean arterial pressure of 70-80 mm Hg. Before pericardium was opened, the end-tidal Isoflurane or

Sevoflurane concentration were stabilized to 1 MAC and then LV diastolic TEE measurements were repeated.

The study data was obtained in 3 steps:

(1) First, the mid-esophageal 4-chamber view was obtained and pulse wave Doppler examination was performed after placing the sample volume at the tips of the mitral valve leaflets. The peak flow velocity of early diastolic filling (E), peak flow velocity of late diastolic filling (A), E/A ratio, A wave duration and deceleration time (DT) for early diastolic filling were acquired.

(2) Second, the pulmonary venous flow velocity was measured on PW Doppler keeping the sample volume in left upper pulmonary vein 0.5-1cm distal to its orifice where it joins the left atrium. Values for the peak systolic flow velocity (S), peak diastolic flow velocity (D), peak reverse atrial flow velocity (Ar) and duration of reverse atrial flow (Ar dur) were obtained.

(3) Third, the tissue Doppler imaging was performed after placing the sample volume at the lateral mitral valve ring. The measurements performed were the peak early diastolic tissue velocity (e') , peak late diastolic tissue velocity (a'), e'/a' ratio, E/e' ratio and isovolumic relaxation time (IVRT).

Three readings were obtained and averaged for each parameter. The study data was collected by retrieving TEE images from the ultrasound machine and manual entering the observations in the study chart.

[A] Preoperative

Demographic data:

(1) Age

(2) Sex

(3) Weight

(4) Height

(5) BSA

Risk factors:

(1) Hypertension

(2) Diabetes

(3) Smoking

(4) COPD/Lung disease

(5) Renal/Hepatic dysfunction

(6) Dyslipidemia

(7) RWMA

(8) LVEF

(9) NYHA class

(10) Preoperative drugs –

Beta blockers, Calcium Channel blockers, Angiotensin Converting Enzyme-Inhibitors, Nitrates, Diuretics.

[B] Intraoperative

Haemodynamic data (every 5 mins)

(1) HR

(2) SBP/DBP/MAP

(3) CVP

(4) SpO_2

(5) BIS value

Echocardiographic data:

(1) E (cm/s)

(2) A (cm/s)

(3) E/A ratio

(4) DT (ms)

(5) Transmitral A duration (ms)

(6) S (cm/s)

(7) D (cm/s)

(8) S/D ratio

(9) Ar (cm/s)

(10) Ar duration (ms)

(11) e’ (cm/s)

(12) a’ (cm/s)

(13) e’/a’ ratio

(14) IVRT (TDI) (ms)

(15) E/e’ ratio

Results obtained from the study are expressed in tabular format.

Binary or ordinal data are expressed as number (%) and continuous numeric variables are expressed as Mean ± SD. Qualitative data was analyzed by Pearson's chi square test or using Fisher exact test, when applicable. Analysis of variance was done for repeated measures of continuous variables by 1 way ANOVA, for post hoc analysis Bonferroni's test was applied. Software used for the analysis was SPSS version 17.0 [SPSS; Chicago IL].

RESULTS

Results obtained from the study are expressed in tabular format.

Binary or ordinal data are expressed as number (%) and continuous numeric variables are expressed as Mean ± SD. Qualitative data was analyzed by Pearson's chi square test or using Fisher exact test, when applicable. Analysis of variance was done for repeated measures of continuous variables by 1 way ANOVA, for post hoc analysis Bonferroni's test was applied. Software used for the analysis was SPSS version 17.0 [SPSS; Chicago IL].

Subjects in Group – I received Isoflurane and subjects in Group – II received Sevoflurane as the test agent.

TABLE 1 : Demographic characteristics

Demographic Characteristics	**Group - I**	**Group - II**
Age (years)	57.81 ± 6.4	59.47 ± 6.8
Sex ratio (% of Males)	76.4	79.1
Body Weight	56.6 ± 6.9	59.2 ± 9.5

There was no significant difference in the demographic characteristics between the two groups.

TABLE 2 : HEMODYNAMIC PARAMETERS AND BIS VALUES (GROUP I)

	0 min	5 min	10 min	15 min	20 min	25 min	30 min	35 min
HR	65 ± 12#	66 ± 12#	68 ± 11#	70 ± 13 #	71 ± 12#	66 ± 10#	68 ± 12#	64 ± 9#
SBP	137±19#	140±17#	142±16#	140±17 #	135±16 #	136±15#	137±15#	136±15#
DBP	82 ±16#	79 ±15#	82± 14#	80 ±13 #	78 ±12#	78± 14#	77 ±13#	76 ±14#
MBP	98 ± 16#	100±18 #	102±21#	100±18 #	97 ±12#	96 ±15#	97 ±13#	96 ±14#
SpO2	99± 0.3#	99± 0.4#	99± 0.4#	99± 0.5#	99± 0.3#	99± 0.7#	99± 0.2#	99 ±0.5#
CVP	7 ±2#	7 ±2.6 #	7± 1.8#	8± 2.3#	8± 2.2#	7± 1.8#	7± 1.7#	8 ±2#
BIS	52± 7·3#	51± 6.8#	51 ±6.1#	49 ±5.3#	49 ±4.6#	48 ±5.3#	48 ±5.5#	49± 5.3#

signifies p>0.05 when compared to baseline (0 min)

TABLE 3 : HEMODYNAMIC PARAME TERS AND BIS VALUES (GROUP II)

	0 min	5 min	10 min	15 min	20 min	25 min	30 min	35 min
HR	65 ±13#	66± 14#	66 ±12#	66± 13#	70 ±14#	68± 15#	69 ±15#	66± 17#
SBP	142±16#	142±14#	140±12#	139±15#	138±16#	137±15#	135±18#	132±16#
DBP	84± 9#	84 ±11#	83± 12#	80 ±14#	80± 16#	79 ±14#	78 ±16#	77 ±14#
MBP	101±12#	101±14#	100±16#	99 ±17#	98 ±18 #	96± 20#	96± 18#	95± 17#
SpO2	99± 0.7#	99± 0.3#	99 ±0.2#	99 ±0.8#	99± 0.6#	99 ±0.8#	99± 0.6#	99± 0.3#
CVP	8± 2.1#	8 ±1.8#	7 ±1.5#	7 ±1.4#	8± 1.4#	8 ±1.6#	8± 2#	8 ±1.4#
BIS	51 ±8 #	50± 7.6#	48 ±8.9#	47± 8#	49 ±8.2#	50 ±8.7#	52± 9#	51 ±6.1#

signifies p>0.05 when compared to baseline (0 min)

There were no significant differences in the hemodynamic parameters (HR, SBP, DBP, MBP, CVP and SpO2) and BIS values in both groups across the various time points.

TABLE 4: Echocardiographic parameters in Group – I (Isoflurane) [n = 25]

TEE MEASUREMENTS	BASELINES	STUDY PERIOD	p value
Transmitral Diastolic Doppler flow profile			
E (cm/s)	48.31 ± 12.12	55.6 +/- 9.67	**0.04***
A (cm/s)	55.05 +/- 12.6	56.23 +/- 11.9	0.86
E / A	0.90 ± 0.33	1.02 ± 0.31	0.16
DT (ms)	223 ± 34	199 ± 33	**0.01***
A duration (ms)	146 ± 20	142 ± 25	0.25
Pulmonary venous flow profile			
S (cm/s)	37.4 ± 9.4	37.5 ± 13.05	0.84
D (cm/s)	23.1 ± 7	27.23 ± 6.3	0.11
S / D	1.65 ± 0.30	1.41 ± 0.47	0.14
Ar (cm/s)	14.3 ± 4.74	21.09 ± 4.51	0.38
Ar duration (ms)	97 ± 25	95 ± 33	0.90
A – Ar duration (ms)	51 ± 19.7	55 ± 27.1	0.77
Tissue Doppler Imaging			
e'(cm/s)	6.41 ± 1.7	6.12 ± 1.4	0.35
a'(cm/s)	8.72 ± 3.34	8.08 ± 2.64	0.24
e'/a'	0.86 ± 0.49	0.84 ± 0.38	0.69
IVRT(TDE) (ms)	129 ± 37	122 ± 24.8	0.70
E/ e'	7.91 ± 2.41	9.4 ± 2.4	**0.04***

(* p < 0.05)

In Group – I (Isoflurane) patients, there was a statistically significant increase in **E** velocity ($p < 0.05$) and the **DT** decreased significantly ($p < 0.05$) towards normal. **A** velocity remained unaltered and **E/A ratio** increased but were not statistically significant. These changes suggest an improvement in LV diastolic relaxation. In the pulmonary venous flow pattern, there was an increase in the diastolic flow velocity **D** which also suggests better LV relaxation. There was no significant change in the TDI parameters. The **E/e'** ratio increased significantly suggesting increased filling pressures but **Ar – A** duration was < 0. Thus the LV filling pressures were probably normal. Thus the results of TMBF and Pulmonary venous flow suggest better LV relaxation but were not supported by corresponding TDI values.

Table 5 : Echocardiographic parameters in Group – II (Sevoflurane) [n = 25]

TEE MEASUREMENTS	BASELINES	STUDY PERIOD	p value
Transmitral Diastolic Doppler flow profile			
E (cm/s)	48.06 ± 10.9	43.26 ± 6.92	0.23
A (cm/s)	56.15 ± 16.2	46.7 ± 12.9	**0.04***
E / A	0.88 ± 0.23	0.97 ± 0.29	0.59
DT (ms)	228 ± 28	196 ± 24	**0.007***
A duration (ms)	143 ± 17	141 ± 20	0.81
Pulmonary venous flow profile			
S (cm/s)	40.7 ± 13.12	38.64 ± 11.4	0.76
D (cm/s)	25.17 ± 8.16	23.17 ± 5.77	0.64
S / D	1.69 ± 0.62	1.72 ± 0.62	0.99
Ar (cm/s)	16.88 ± 4.1	14.8 ± 4.45	0.66
Ar duration (ms)	96 ± 25	95 ± 23	0.40
A – Ar duration (ms)	47 ± 27.2	45 ± 27.9	0.40
Tissue Doppler Imaging			
e'(cm/s)	8.02 ± 2.17	6.69 ± 1.91	**0.01***
a'(cm/s)	8.37 ± 2.77	6.47 ± 1.39	**0.04***
e'/a'	1.05 ± 0.44	1.10 ± 1.39	0.83
IVRT(TDE) (ms)	123 ± 29	124 ± 26	0.77
E/ e'	6.30 ± 1.89	6.77 ± 2.07	0.18

(* $p < 0.05$)

In Group – II (Sevoflurane) patients, the TMBF Doppler velocities showed an decrease in **E** and **A** (statistically significant, $p < 0.05$), while the E/A ratio increased slightly. The DT decreased significantly ($p < 0.05$). The TDI parameters **e'** and **a'** decreased significantly ($p < 0.05$). The TMBF velocities suggest improvement in LV relaxation since **E/A ratio** slightly increased towards normal and DT decreased. But the **E** velocity decreased which was associated with corresponding decrease in Pulmonary venous **D** velocity and **e'** velocity, suggesting a possible deterioration of LV relaxation. Reduction in **A** and **a'** suggests decreased LA contractility.

Previous studies suggested that there may be different responses to inhalational anesthetics in patients with normal diastolic function, when compared with those with diastolic dysfunction. So in the present study, we separately evaluated the changes in diastolic function in patients with Normal diastolic function and those with Grade I Diastolic dysfunction (impaired relaxation).

TABLE 6 : Echocardiographic parameters in patients in Group – I (Isoflurane) with normal diastolic function. [n = 18]

TEE MEASUREMENTS	BASELINES	STUDY PERIOD	p value
Transmitral Diastolic Doppler flow profile			
E (cm/s)	52.49 ± 16.18	56.64 ± 11.61	0.33
A (cm/s)	51.08 ± 13.02	48.11 ± 10.16	0.56
E / A	1.05 ± 0.36	1.20 ± 0.29	0.15
DT (ms)	213 ± 37.6	202 ± 34	0.65
A duration (ms)	151 ± 21	139 ± 21	0.19
Pulmonary venous flow profile			
S (cm/s)	37.9 ± 8.5	36.5 ± 13.5	0.60
D (cm/s)	24.04 ± 7.25	27 ± 8.3	0.66
S / D	1.65 ± 0.44	1.47 ± 0.72	0.75
Ar (cm/s)	13.11 ± 4.26	13.02 ± 5.5	0.48
Ar duration (ms)	104 ± 23	102 ± 36.23	0.76
A – Ar duration (ms)	50 ± 26.7	44 ± 27.8	0.63
Tissue Doppler Imaging			
e'(cm/s)	7.40 ± 1.99	7.23 ± 2.18	0.95
a'(cm/s)	7.75 ± 2.94	7.09 ± 2.63	0.63
e'/a'	1.06 ± 0.43	1.12 ± 0.44	0.80
IVRT(TDE) (ms)	129 ±33.6	120 ± 29	0.32
E/ e'	7.5 ± 2.9	8.6 ± 3.6	0.31

(* $p < 0.05$)

There was increase in **E**, decrease in **A** and **DT**; but none were statistically significant. Both **e'** and **a'** decreased but was not statistically significant. Thus in this patient group , there was an apparent improvement in LV relaxation in TMBF velocities but the TDI parameters did not show corresponding changes.

TABLE 7 : Echocardiographic parameters in patients in Group – I (Isoflurane) with Grade - I diastolic dysfunction (impaired relaxation). [n = 7]

TEE MEASUREMENTS	BASELINES	STUDY PERIOD	p value
Transmitral Diastolic Doppler flow profile			
E (cm/s)	44.94 ± 8.61	56.7 ± 11.4	**0.05***
A (cm/s)	64.32 ± 11.06	63.02 ± 11.19	0.83
E / A	0.70 ± 0.13	0.84 ± 0.20	0.16
DT (ms)	242 ± 28	197 ± 22	**0.006***
A duration (ms)	137 ± 15.5	142 ± 35	0.72
Pulmonary venous flow profile			
S (cm/s)	34.7 ± 7.3	40.58 ± 9.8	0.23
D (cm/s)	19.7 ± 4.67	27.07 ± 7.1	**0.04***
S / D	1.77 ± 0.26	1.5 ± 0.24	0.08
Ar (cm/s)	15.87 ± 6.3	14.2 ± 3..9	0.56
Ar duration (ms)	84.5 ± 18.37	88 ± 19.38	0.73
A – Ar duration (ms)	52 ± 23.8	56 ± 34.2	0.80
Tissue Doppler Imaging			
e'(cm/s)	5.14 ± 0.83	5.56 ± 1.09	0.43
a'(cm/s)	10.24 ± 2.7	9.53 ± 1.27	0.54
e'/a'	0.51 ± 0.10	0.58 ± 0.10	0.25
IVRT(TDE) (ms)	120 ± 35	111 ± 11.1	0.55
E/ e'	8.9 ± 2.3	9.9 ± 1.8	0.39

(* $p < 0.05$)

In patients with pre-existing impaired LV relaxation, there was a greater increase in **E** than patients with normal diastolic function, which was, statistically significant. The corresponding increase in diastolic flow in pulmonary veins **D** was also statistically significant. The **DT** also decreased significantly. Thus, isoflurane caused statistically significant improvement in LV relaxation in TMBF velocities, which was supported by favorable pulmonary venous flow patterns. But these changes were not reflected in the TDI parameters.

TABLE 8 : Echocardiographic parameters in patients in Group – II (Sevoflurane) with normal diastolic function. [n = 17]

TEE MEASUREMENTS	BASELINES	STUDY PERIOD	p value
Transmitral Diastolic Doppler flow profile			
E (cm/s)	48.9 ± 9.02	43.7 ± 4.46	0.12
A (cm/s)	54.3 ± 15.9	44.89 ± 15.87	0.12
E / A	0.93 ± 0.22	1.04 ± 0.30	0.27
DT (ms)	221 ± 20	195 ± 24.88	**0.008***
A duration (ms)	145 ± 17.9	141 ± 19.9	0.87
Pulmonary venous flow profile			
S (cm/s)	40.55 ± 13.4	38.53 ± 13.06	0.77
D (cm/s)	25 ± 7.89	23.04 ± 5.48	0.63
S / D	1.7 ± 0.69	1.69 ± 0.63	0.91
Ar (cm/s)	15.6 ± 3.67	13.5 ± 3.9	0.21
Ar duration (ms)	95 ± 27	96 ± 23	0.39
A – Ar duration (ms)	50 ± 26.2	45 ± 22.7	0.38
Tissue Doppler Imaging			
e'(cm/s)	8.7 ± 1.8	7.02 ± 2.1	**0.04***
a'(cm/s)	7.97 ± 2.94	6.16 ± 1.38	**0.03***
e'/a'	1.19 ± 0.39	1.21 ± 0.41	0.61
IVRT(TDE) (ms)	121 ± 21.5	123 ± 21.45	0.89
E/ e'	5.78 ± 1.6	6.4 ± 1.88	0.32

(* p < 0.05)

In subjects with normal diastolic function, there was decrease in TMBF velocities **E** and **A** which was not statistically significant, but decrease in DT was statistically significant. **E/A** ratio were increased. The TDI velocities **e'** and **a'** both decreased significantly. Thus although TMBF velocities suggested that LV relaxation may have improved slightly, but TDI parameters show significant deterioration in both early and late diastolic filling.

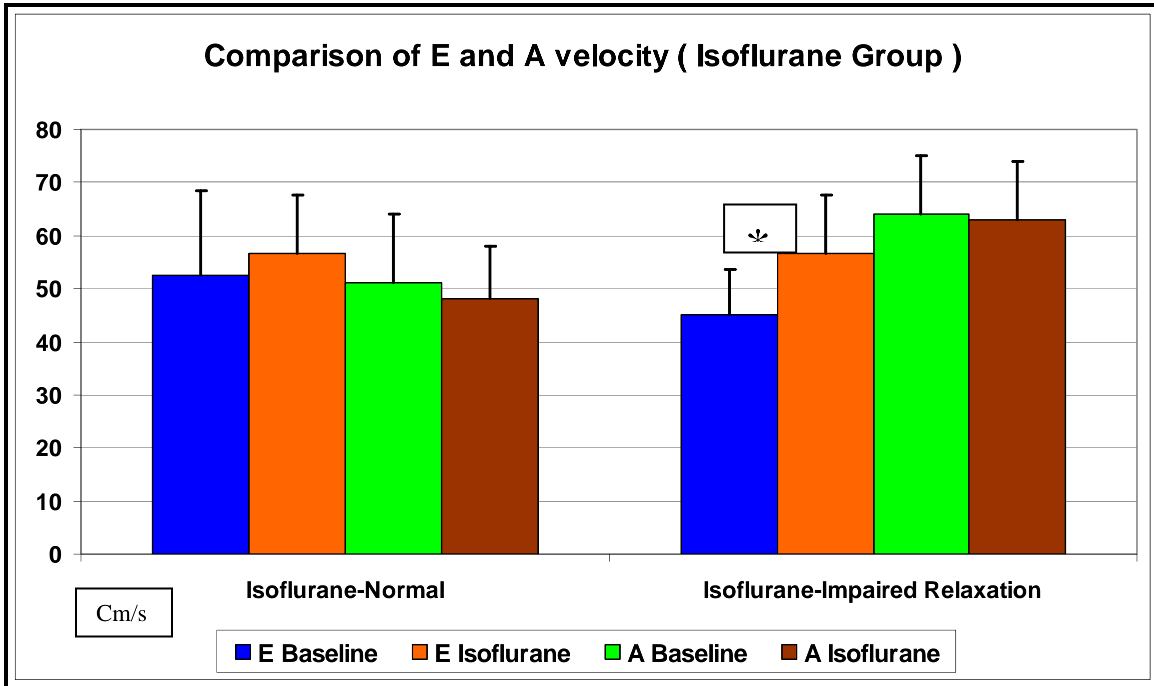
TABLE 9 : Echocardiographic parameters in patients in Group – II (Sevoflurane) with Grade - I diastolic dysfunction (impaired relaxation). [n = 8]

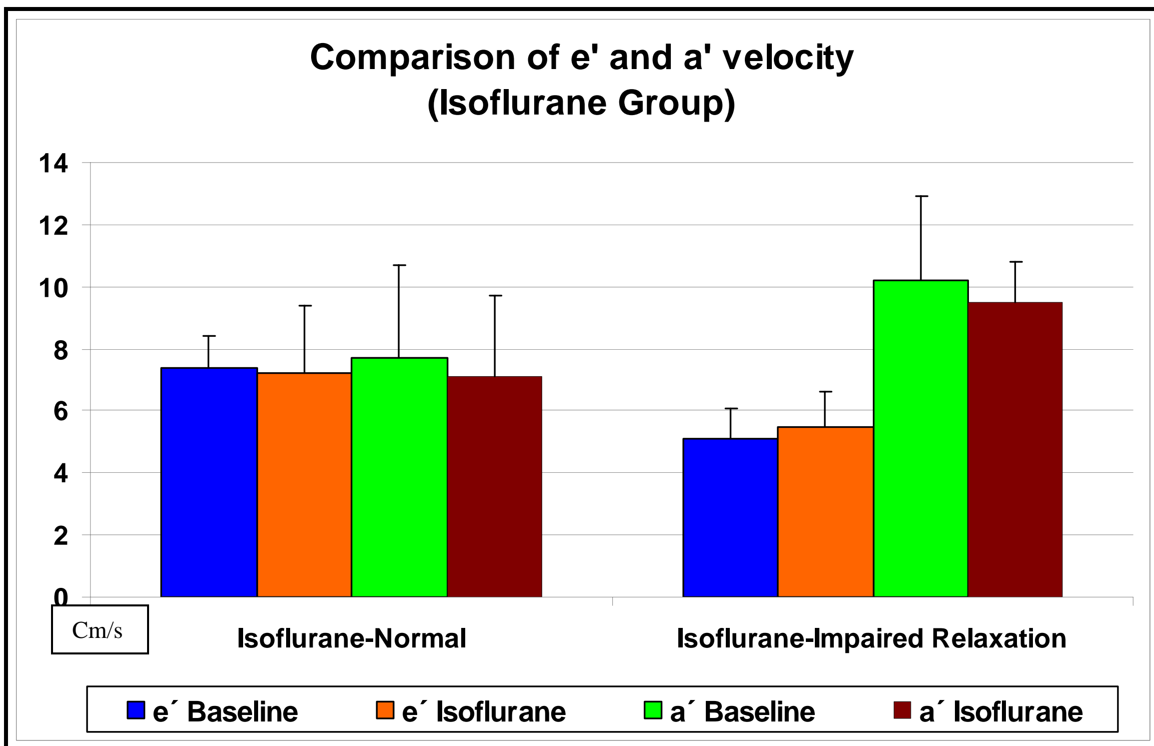
TEE MEASUREMENTS	BASELINES	STUDY PERIOD	p value
Transmitral Diastolic Doppler flow profile			
E (cm/s)	44.61 ± 13.8	36.74 ± 12.46	0.28
A (cm/s)	57.34 ± 15.46	45.5 ± 11.84	0.13
E / A	0.78 ± 0.17	0.8 ± 0.16	0.85
DT (ms)	249 ± 30	193 ± 21	**0.002***
A duration (ms)	136 ± 12	140 ± 19	0.56
Pulmonary venous flow profile			
S (cm/s)	38.04 ± 10.9	34.28 ± 6.97	0.4
D (cm/s)	24.88 ± 7.63	21.4 ± 6.57	0.38
S / D	1.56 ± 0.34	1.74 ± 0.65	0.55
Ar (cm/s)	17.7 ± 4.65	14.8 ± 6.10	0.33
Ar duration (ms)	93 ± 21	98 ± 21	0.68
A – Ar duration (ms)	41 ± 29.6	42 ± 33.7	0.9
Tissue Doppler Imaging			
e'(cm/s)	4.95 ± 1.23	4.90 ± 1.03	0.93
a'(cm/s)	8.73 ± 1.77	6.45 ± 1.82	**0.03***
e'/a'	0.56 ± 0.08	0.80 ± 0.27	**0.04***
IVRT(TDE) (ms)	142 ± 46	135 ± 34	0.73
E/ e'	9.07 ± 1.95	7.53 ± 2.33	0.20

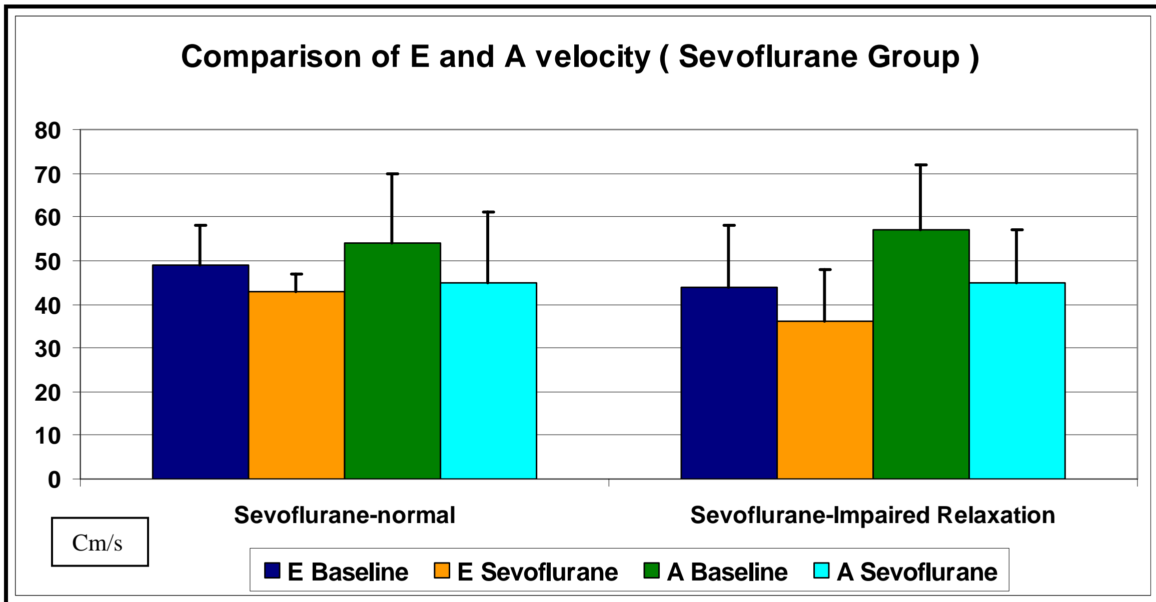
(* $p < 0.05$)

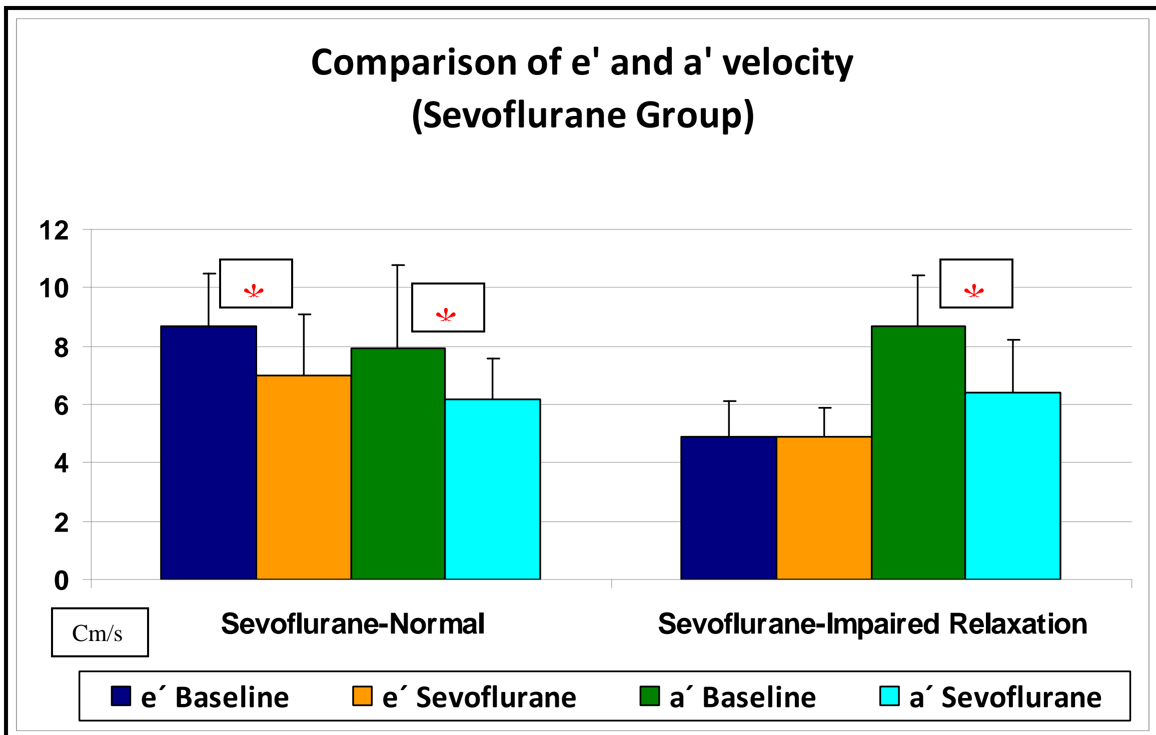
In this group, the decrease in **DT** was significant. **E** and **A** decreased but not significantly. The **E/A** ratio were unchanged. In the TDI parameters, only **a’** decreased significantly and not **a’**. Therefore the **e’/a’** increased significantly. Thus in patients with pre-existing impaired relaxation, there was minimal change in early ventricular filling indices. But late diastolic filling is significantly impaired probably due to impaired LA contractility.

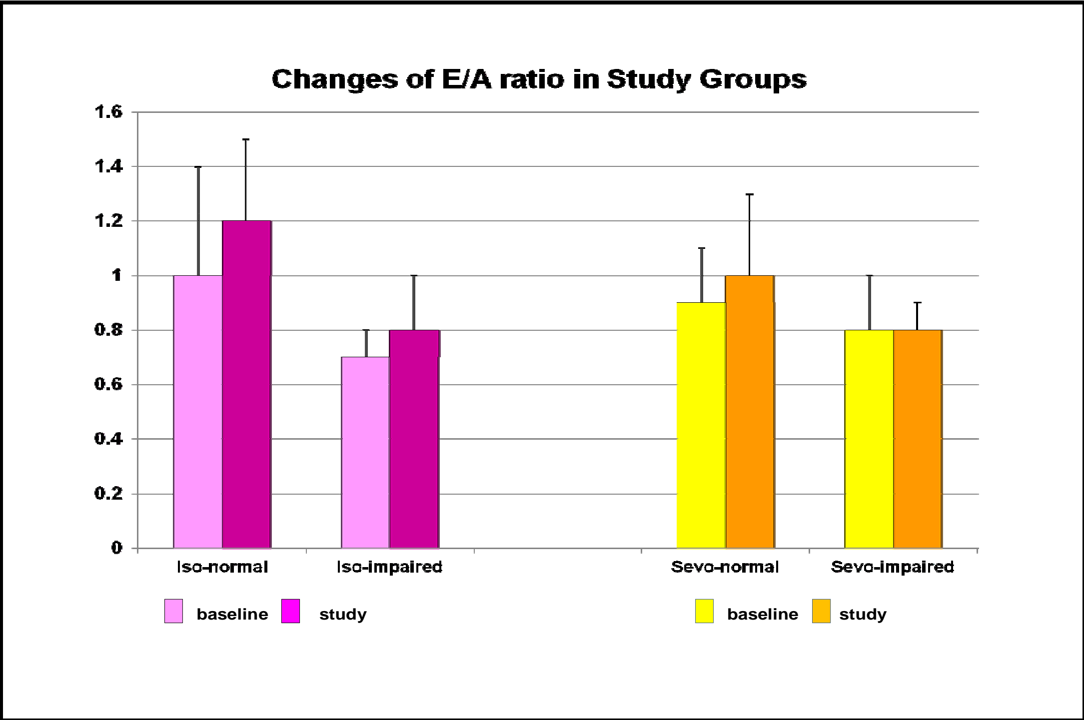
DIAGRAMS

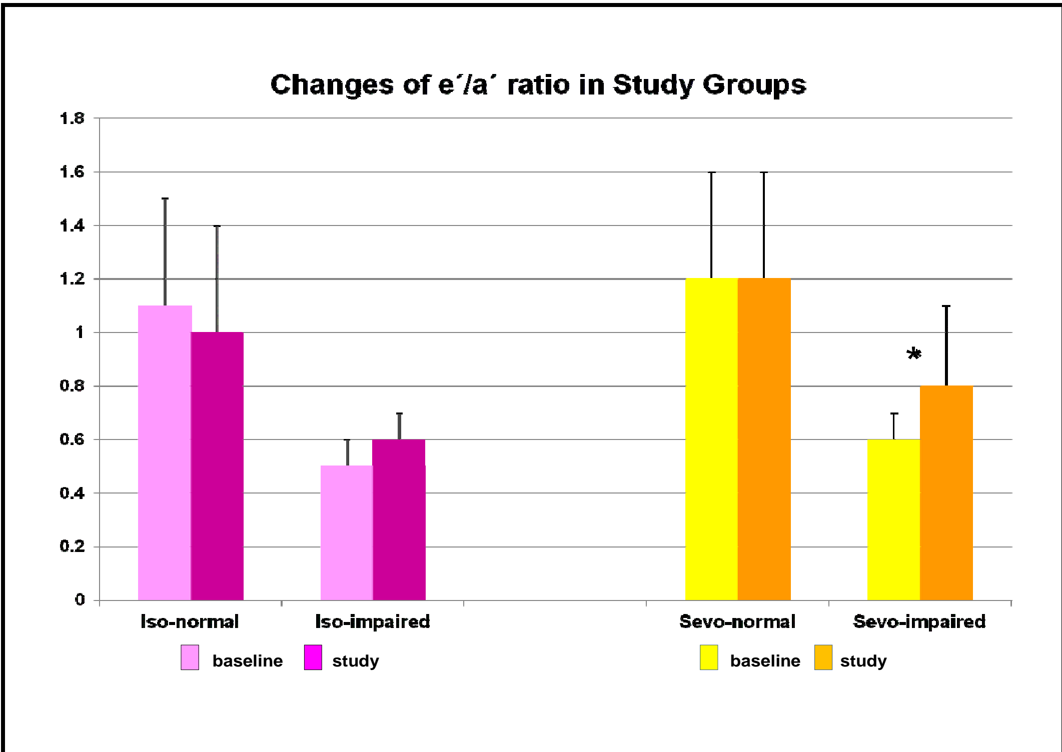





Comparison of E and A velocity (Sevoflurane Group)
80
70
60
50
40
30
20
10
0
Sevoflurane-normal
Sevoflurane-Impaired Relaxation
Cm/s
E Baseline
E Sevoflurane
A Baseline
A Sevoflurane


Comparison of e' and a' velocity
(Sevoflurane Group)
12
10
8
6
4
2
0
Sevoflurane-Normal
Sevoflurane-Impaired Relaxation
Cm/s
e´ Baseline
e´ Sevoflurane
a´ Baseline
a´ Sevoflurane


Changes of E/A ratio in Study Groups
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Iso-normal
Iso-impaired
Sevo-normal
Sevo-impaired
baseline
study
baseline
study


Changes of e´/a´ ratio in Study Groups
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
*
Iso-normal
Iso-impaired
Sevo-normal
Sevo-impaired
baseline
study
baseline
study

DISCUSSION

Isoflurane and Sevoflurane are indispensable constituents of the balanced anesthesia techniques used in cardiac anesthesia. Previous animal studies have pointed out that both Isoflurane and Sevoflurane have detrimental effects on LV diastolic function. Human studies evaluating the effect of Isoflurane and Sevoflurane on LV diastolic function have been inconclusive. Against this background, this intra-operative study was designed to quantify and compare the effects of Isoflurane and Sevoflurane on LV diastolic function, assessed with the help of TEE, during the pre- CPB period in patients with IHD undergoing on pump CABG.

Echocardiography with Doppler utilizes four methods to determine diastolic function.

(1) Transmitral diastolic blood flow profile

(2) Pulmonary venous blood flow profile

(3) Tissue Doppler Imaging (TDI)

(4) Colour M - mode transmitral flow propagation velocity (Vp)

Although, the Vp is considered to be a preload independent parameter for the assessment of LV diastolic function, the TDI has been found to be superior to the Vp measurement in this respect. Tomas Palecek et al [31] measured early diastolic septal mitral annular velocity (e') determined by PW-TDI and color M-mode flow propagation velocity (Vp) in 86 male patients and compared them with LV filling patterns obtained using standard Doppler indices. They concluded that e' was superior to Vp in the detection of mild to

moderate LV diastolic dysfunction.. Vp failed to detect abnormal LV diastolic function, in patients with preserved LV systolic function and a pseudonormal filling pattern type.

Bess et al [32] observed that a major limitation to use Vp in the assessment of LV diastolic function is that there is currently no one agreed-upon definition or method for measuring Vp. They also noted that the propagation of the filling wave front may sometimes be blurred, making it difficult to determine its margin. Vp can be technically challenging to perform and even more difficult to interpret. Further more, the complexity of intraventricular flow and the limitations of current imaging techniques make it difficult to relate intraventricular flow patterns to LV myocardial function in a quantitative manner, as while measuring the Vp [13].

De Boeck BW et al [33] observed that it may not be possible to measure Vp because the slope of flow propagation is sometimes curvilinear and does not “travel” a sufficient distance (4 cm) into the LV cavity or is difficult to appreciate. They also stated that an abnormal Vp merely diagnoses the presence of abnormal relaxation, and not necessarily its severity. Therefore, an abnormal Vp may not differentiate among the various stages of abnormal and worsening of diastolic function

The two major principles of fluid dynamics predicting the characteristics of fluid propagation in the left ventricle during diastole are pressure gradient and vortex formation. Both of them are modified by left ventricular geometry and synchrony of wall

relaxation. Alterations in chamber geometry, contractile dyssynchrony, and complex blood flow vortex formation may limit the use of Vp as a quantitative index.[13]

.

Thus, in view of the technical difficulties in obtaining an accurate Vp and the inherent limitations of Vp, we have excluded measurement of Vp from our study.

Traditionally, transmitral flow velocity parameters have been used to assess LV diastolic function. However, these parameters are altered by various perioperative factors like patient age, heart rate and rhythm, loading conditions, location of the Doppler sample volume, and ultrasound equipment settings. The utility of the TMBF echocardiographic parameters throughout the perioperative period is limited by the unavoidable effects of changes in preload, afterload, heart rate, and rhythm on peak velocities and proportions of early and late filling [34]. Hence relying solely on transmitral flow velocity parameters may result in errors in the evaluation of LV diastolic function. Before interpreting the results, it becomes necessary to correlate the TMBF parameters with another modality, which will be least influenced by these factors. Sohn et al [35] showed that TDI parameters E' and E'/A' ratio did not change significantly after preload alterations with saline infusion or nitroglycerine. Tissue Doppler imaging parameters, being independent of loading condition, can help to differentiate between normal patients and those with pseudonormal LV filling.

LV diastolic function is graded as

(1) Normal

(2) Grade I diastolic dysfunction (Impaired relaxation)

(3) Grade II diastolic dysfunction (Pseudo normal filling pattern)

(2) Grade III diastolic dysfunction (Restrictive filling)

In the present study, we have included those with Normal diastolic function and Grade I diastolic dysfunction. Grade II & III diastolic dysfunction were excluded from the study.

In patients with Normal diastolic function,

- E/A > 1
- DT < 220ms
- IVRT <100ms
- S/D > / = 1
- Ar velocity < 35 cm/sec and duration 90 - 115 msec.
- Ar < A duration (120 -140 msec)
- e' > 8 cm/sec.

In patients with Grade I diastolic dysfunction (Impaired relaxation), the rate of pressure drop between LA and LV is slowed manifested by decrease in peak E velocity. The early LV filling is prolonged , producing increased DT. The atrial contraction force increases to compensate leading to increased peak A velocity. Thus the E/A ratio becomes <1.The

pulmonary venous flow shows reduced D velocity and compensatory increased S velocity resulting in Systolic dominance. Thus,

- E/A ratio <1
- Prolongation of DT (DT > 220 milliseconds),
- IVRT < 100 msec
- S/D ratio remains > > 1 expressing decreased early diastolic flow,
- e' <8cm/sec.

Analysis of results of the study:

Isoflurane Group

In our study, we observed that in ***patients with normal diastolic function***, 1 MAC isoflurane does not cause any measurable change in diastolic function indices. Patients with normal diastolic function who were administered 1 MAC isoflurane had a small increase in E, decrease in A, increased E/A ratio and decreased DT. But none reached statistical significance. There were no significant corresponding changes in pulmonary venous flow profile and TDI parameters. Our findings are consistent with other previously published studies (Oxorn and Bolliger). Oxorn et al [26], reported in their study in healthy patients undergoing peripheral orthopedic surgery, isoflurane anesthesia at MAC 1 and MAC 1.5 resulted in decreased velocity of transmitral flow during atrial systole (A velocity), shortening of the deceleration time of early diastolic transmitral flow (E velocity), and preservation of pulmonary venous velocities as measured by Doppler echocardiography. There were no significant changes in PV flow velocities and TDI

measurements. Bolliger et al [30] also noted that isoflurane did not cause impairment of LV diastolic function in normal subjects during spontaneous ventilation and IPPV.

In ***patients with Grade I diastolic dysfunction***, an apparent improvement in early diastolic filling was seen. The TMBF and pulmonary venous flow profiles suggested an improvement in the indices of diastolic function, although, these changes are not reflected in TDI measurements.

In patients with Grade I diastolic dysfunction, we observed a statistically significant increase in E ($p < 0.05$), small decrease in A, increased E/A and a statistically significant decrease in DT ($p < 0.05$). The increased E was reflected in the PV flow velocity where there was a statistically significant increase in D velocity ($p < 0.05$). The D wave velocity is dependent on LV compliance and the extent of early LV filling. But there were no significant corresponding changes in TDI parameters. Thus, a discrepancy was noted in the observations of TMBF, Pulmonary venous and TDI parameters.

Although the TMBF and pulmonary venous flow alterations suggest an improvement in the indices of diastolic function (i.e. increased E, decreased DT and increased E/A, increased D), the changes are not reflected in TDI measurements. Thus, the changes may be attributed to changes in preload and afterload due to isoflurane rather than due to improvement in LV relaxation, since TDI measurements are less affected by changes in loading conditions.

Similarly Neuhauser et al [27] , in their study in patients with diastolic dysfunction due to concentric hypertrophy and ischemic heart disease , noted that there was an increase in E leading to a larger E/A ratio and DT decreased with isoflurane. This was also accompanied by increases in e' and e'/a' ratio in the tissue Doppler pattern as well as decrease in the IVRT. They concluded that changes in loading conditions as well as the inotropic state are more likely to cause the LV to operate on a steeper region of the pressure-volume curve, rather than direct alterations of the intrinsic viscoelastic properties of the myocardium.

Thus, we observed that 1 MAC isoflurane does not cause any significant change in diastolic function in patients with normal diastolic function and impaired relaxation. An apparent improvement in early diastolic filling may be seen, which is more evident in patients with impaired relaxation, and may be attributed to changes in loading conditions rather than due to any direct effect on myocardial relaxation properties.

Sevoflurane group

In ***patients with normal diastolic function***, sevoflurane resulted in significant deterioration in both early and late diastolic filling. Sevoflurane decreased E and A velocities in TMBF profile. There was a statistically significant decrease in DT ($p < 0.05$). There was also a statistically significant decrease in e' and a' ($p < 0.05$). The PV diastolic velocity D also decreased. The observation is similar to that of Bolliger D et al[30] who observed in their study on the effects of sevoflurane, desflurane, and isoflurane on early and late left ventricular diastolic function in young healthy adults, that there was

decreased E, A, e’ and a’. In contrast to Isoflurane group, the changes in TMBF are also accompanied by significant corresponding changes in TDI measurements. So sevoflurane probably impairs both early and late diastolic function.

Bolliger D et al [30] opined that the sympathoadrenergic effects of desflurane and isoflurane could have resulted in better diastolic performance compared with sevoflurane. However since e’ was within the normal range in the sevoflurane group in their study, they suggested that sevoflurane might not have a clinically relevant direct effect on early diastolic function in healthy individuals. Late diastolic filling due to atrial contraction was significantly depressed by all 3 agents.

In our study the decrease in e’ was below the normal range (i.e. 8 cm/sec). Thus there was a significant impairment in early diastolic filling due to sevoflurane in our study. Sevoflurane also impaired late diastolic filling which was probably due to depressed LA contraction.

In ***patients with Grade I diastolic dysfunction***, the early diastolic filling is not much affected by sevoflurane but late diastolic filling is significantly depressed. There was decreased E and A and E/A ratio was unchanged. There was a statistically significant decrease in DT. Among the TDI parameters, the e’ was not altered but the a’ decreased significantly. Thus the e’/a’ increased.

The observations are similar to Filipovic M et al [29] who studied the effects of sevoflurane and propofol on left ventricular diastolic function in patients with pre-existing diastolic dysfunction. They observed that during anesthesia and IPPV, there was no difference in e' between the study groups. During spontaneous breathing and consecutive elevation of end tidal carbon dioxide, sevoflurane slightly improved early diastolic function whereas propofol had no detectable effect. In contrast, during IPPV and normal end-tidal carbon dioxide the early diastolic function in both the groups was similarly impaired. They also noted that Sevoflurane impaired systolic atrial and ventricular functions, as indicated by decreases of s' and a'.

Thus we observed that in patients with impaired relaxation, the early diastolic filling is not much affected by sevoflurane. But late diastolic filling is significantly depressed.

The clinical consequences of our findings

The objective of our study was to evaluate whether the Isoflurane and Sevoflurane adversely affect echocardiographic parameters of LV diastolic function and to compare the effects of Isoflurane and Sevoflurane on echocardiographic LV diastolic parameters. After analyzing the results it may be concluded that the alterations in LV diastolic function is variable and depends not only on the inhalational agent administered (isoflurane versus sevoflurane), but also on whether the patient has normal diastolic function or diastolic dysfunction.

Isoflurane does not significantly alter LV diastolic function in patients with normal diastolic function and impaired relaxation. An apparent improvement in early diastolic filling may be seen, which is more evident in patients with impaired relaxation, which may be attributed to changes in loading conditions.

Sevoflurane causes significant impairment in late diastolic filling in both patients with normal diastolic function as well as impaired relaxation. Sevoflurane also impairs early diastolic filling, more significantly in patients with normal diastolic function.

These findings have significant clinical implications.

- Isoflurane has no significant effect on LV relaxation in patients with normal diastolic function. In patients with impaired relaxation, isoflurane favorably affects early diastolic filling and should be the preferred inhalational agent (compared to sevoflurane).
- In patients like severe aortic stenosis, who are very much dependent on atrial kick for adequate LV filling, sevoflurane is better avoided due to its significant impairment of late diastolic filling.

Limitations of the present study

1. The study was adequately powered for the evaluation of changes in diastolic function in CABG patients with normal diastolic function or mild (Grade I) diastolic dysfunction. Initially our objective was not to evaluate them as separate groups based on the pre-operative transthoracic echocardiogram (TTE) because

- There may be considerable inter-observer variability in the observations of the cardiologist and the intra-operative echocardiographer.
- All pre-operative TTE observations could not be recorded and detailed evaluation of diastolic function with TDI in all patients was not possible in the pre-operative TTE evaluation in the busy OPD.
- It was questionable whether pre-operative TTE recordings could be considered as baseline values for comparison with subsequent intra-operative TEE recordings.

So we retrospectively divided the patients into groups with Normal diastolic function and Impaired relaxation. Our conclusion on the effects of inhalational agents in patients with impaired relaxation was thus based on a smaller sample size (Isoflurane n = 8 ; Sevoflurane n = 7). Further studies with larger number of patients with impaired relaxation may be required to improve the level of evidence.

2. It is a non-blinded study. Blinding was not feasible in our operating room set-up since the vaporizers and anesthetic gas monitors could not be masked from the echocardiographer.

3. The control values were taken in all the patients in the study in both the groups under anesthesia maintained with propofol. Previous studies by Filipovic et al [29] have shown that propofol does cause some diastolic dysfunction. But the impairment of diastolic function by propofol was mild and did not cause clinical diastolic dysfunction in any of the subjects. Thus the effects of propofol on diastolic function were probably minimal and would have affected both groups equally.

CONCLUSION

The conclusions of the study are:

(1) Isoflurane and Sevoflurane administered in 1 MAC, to patients with normal diastolic function or Grade I diastolic dysfunction undergoing CABG, were found to affect the echocardiographic diastolic parameters assessed by TEE. Isoflurane was not found to have any adverse effects on LV diastolic function. Sevoflurane was found to impair LV diastolic function in patients with normal diastolic function and Grade I diastolic dysfunction.

(2) Comparison of the effects of Isoflurane and Sevoflurane on LV diastolic function showed that:

- Sevoflurane impairs LV diastolic function while Isoflurane has negligible effects on it.
- Isoflurane does not significantly alter LV diastolic function in patients with normal diastolic function and impaired relaxation.
- Isoflurane causes an apparent improvement in early diastolic filling, which is more evident in patients with impaired relaxation. It may be attributed to changes in loading conditions.
- Sevoflurane impairs early diastolic filling, more significantly in patients with normal diastolic function.

- Sevoflurane causes significant impairment in late diastolic filling in both patients with normal diastolic function as well as impaired relaxation.

REFERENCES

1. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007; 28: 2539-50.

2. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009; 22:107–33

3. Denault AY, Couture P, Buithieu J, Haddad F, Carrier M, Babin D, Levesque S, Tardif JC. Left and right ventricular diastolic dysfunction as predictors of difficult separation from cardiopulmonary bypass. Can J Anesth 2006; 53:1020–9.

4. Flu WJ, van Kuijk JP, Hoeks SE, Kuiper R, Schouten O, Goei D, Elhendy A, Verhagen HJ, Thomson IR, Bax JJ, Fleisher LA, Poldermans D. Prognostic implications of asymptomatic left ventricular dysfunction in patients undergoing vascular surgery. Anesthesiology 2010; 112:1316–24

5. Matyal R, Hess PE, Subramaniam B, Mitchell J, Panzica PJ, Pomposelli F, Mahmood F. Perioperative diastolic dysfunction during vascular surgery and its association with postoperative outcome. J Vasc Surg 2009; 50:70–6.

6. Nanhi Mitter, Kelly Grogan, Daniel Nyhan, Dan E. Berkowitz. Pharmacology of Anesthetic drugs. In: Joel A. Kaplan, David L. Reich, Joseph S. Savino (editors) Kaplan's Cardiac Anesthesia: The Echo Era, Sixth Edition, 2011, Elsevier Saunders, St. Louis, Missouri, Pg: 193 – 200.

7. Robina Matyal, Nikolaos J. Skubas, Stanton K. Shernan, and Feroze Mahmood. Perioperative Assessment of Diastolic Dysfunction. Anesth Analg 2011; 113:449 –72.

8. Pagel PS, Kampine JP, Schmeling WT, Warltier DC. Alteration of left ventricular diastolic function by desflurane, isoflurane, and halothane in the chronically instrumented dog with autonomic nervous system blockade. Anesthesiology 1991; 74:1103–14

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

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

11. Ronald A. Kahn, Nikolaos J. Skubas, Gregory W. Fischer, Stanton K. Shernan,Steven N. Konstadt. Intra-operative Transesophageal Echocardiography. In: Joel A. Kaplan, David L. Reich, Joseph S. Savino (editors), Kaplan's Cardiac Anesthesia: The Echo Era, Sixth Edition, 2011, Elsevier Saunders, St. Louis, Missouri, Pg:315-355.

12. Paul. S Pagel. Cardiac Physiology. In: Joel A. Kaplan, David L. Reich, Joseph S. Savino (editors) Kaplan's Cardiac Anesthesia: The Echo Era, Sixth Edition, 2011, Elsevier Saunders, St. Louis, Missouri, Pg: 121-123.

13. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009; 22:107–33.

14. Garcia M, Thomas J, Klein A. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 1998; 32: 872.

15. Robina Matyal, Nikolaos J. Skubas, Stanton K. Shernan, and Feroze Mahmood. Perioperative Assessment of Diastolic Dysfunction. Anesth Analg 2011; 113:449 –72.

16. Doyle RL, Foëx P, Ryder WA, Jones LA. Effects of halothane on left ventricular relaxation and early diastolic coronary blood flow in the dog. Anesthesiology 1989 Apr;70(4):660-6.

17. Humphrey LS, Stinson DC, Humphrey MJ, Finney RS, Zeller PA, Judd MR, Blanck TJ.Volatile anesthetic effects on left ventricular relaxation in swine. Anesthesiology. 1990 Oct; 73(4):731-8.

18. Pagel PS, Kampine JP, Schmeling WT, Warltier DC.Alteration of left ventricular diastolic function by desflurane, isoflurane, and halothane in the chronically instrumented dog with autonomic nervous system blockade. Anesthesiology. 1991 Jun; 74(6):1103-14.

19. Pagel PS, Kampine JP, Schmeling WT, Warltier DC.Reversal of volatile anesthetic-induced depression of myocardial contractility by extracellular calcium also enhances left ventricular diastolic function. Anesthesiology. 1993 Jan; 78(1):141-54.

20. Harkin CP, Pagel PS, Kersten JR, Hettrick DA, Warltier DC.Direct negative inotropic and lusitropic effects of sevoflurane. Anesthesiology. 1994 Jul; 81(1):156-67.

21. Pagel PS, Hettrick DA, Lowe D, Tessmer JP, Warltier DC. Desflurane and isoflurane exert modest beneficial actions on left ventricular diastolic function during myocardial ischemia in dogs. Anesthesiology. 1995 Nov; 83(5):1021-35.

22. Yamada T, Takeda J, Koyama K, Sekiguchi H, Fukushima K, Kawazoe T.Effects of sevoflurane, isoflurane, enflurane, and halothane on left ventricular diastolic performance in dogs. J Cardiothorac Vasc Anesth. 1994 Dec; 8(6):618-24.

23. M. Ruth Graham , Darren B. Thiessen , W. Alan C. Mutch . Isoflurane and halothane impair both systolic and diastolic function in the newborn pig. Can J Anesth 1996 ;43(5) 495-502

24. Hanouz JL, Vivien B, Gueugniaud PY, Lecarpentier Y, Coriat P, Riou B. Comparison of the effects of sevoflurane, isoflurane and halothane on rat myocardium. Br J Anaesth. 1998 May; 80(5):621-7.

25. Houltz E, Caidahl K, Adin C, Gustavsson T, Ricksten SE.Effects of halothane and isoflurane on left ventricular diastolic function during surgical stress in patients with coronary artery disease. Acta Anaesthesiol Scand. 1997 Aug; 41(7):931-8.

26. Oxorn D, Edelist G, Harrington E, Tsang S.Echocardiographic assessment of left ventricular filling during isoflurane anaesthesia. Can J Anaesth. 1996 Jun; 43(6):569-74.

27. Christoph Neuhäuser, Matthias Müller, Ingeborg Welters, Stefan Scholz, and Myron M. Kwapisz, Effect of Isoflurane on Echocardiographic Left-Ventricular Relaxation Indices in Patients With Diastolic Dysfunction Due to Concentric Hypertrophy and Ischemic Heart Disease. Journal of Cardiothoracic and Vascular Anesthesia, Vol 20, No 4 (August), 2006: pp 509-514

28. M. Filipovic, J. Wang, I. Michaux, P. Hunziker, K. Skarvan and M. D. Seeberger Effects of halothane, sevoflurane and propofol on left ventricular diastolic function in humans during spontaneous and mechanical ventilation. British Journal of Anesthesia 94 (2): 186–92 (2005)

29. M. Filipovic, I. Michaux, J. Wang, P. Hunziker, K. Skarvan and M. Seeberger Effects of sevoflurane and propofol on left ventricular diastolic function in patients with pre-existing diastolic dysfunction. British Journal of Anesthesia 98 (1): 12–18 (2007)

30. D. Bolliger, M. Seeberger, J. Kasper, A. Bernheim, R. M. Schumann, K. Skarvan, P. Buser and M. Filipovic Different effects of sevoflurane, desflurane, and isoflurane on early and late left ventricular diastolic function in young healthy adults
British Journal of Anesthesia 104 (5): 547–54 (2010)

31. Tomas Palecek, Ales Linhart, Jan Bultas, Michael Aschermann. Comparison of early diastolic mitral annular velocity and flow propagation velocity in detection of mild

to moderate left ventricular diastolic dysfunction. Eur J Echocardiography (2004) 5 ; 196 – 204.

32. Renee L. Bess , Shahabuddin Khan, , Howard S. Rosman , Gerald I. Cohen , Zuhair Allebban, Julius M. Gardin. Technical Aspects of Diastology: Why Mitral Inflow and Tissue Doppler Imaging Are the Preferred Parameters? Echocardiography Vol. 23, No. 4, 2006.

33. De Boeck BW, Oh JK, Vandervoort PM, Vierendeels JA, van der Aa RP, Cramer MJ. Colour M-mode velocity propagation: a glance at intra-ventricular pressure gradients and early diastolic ventricular performance. Eur J Heart Fail 2005; 7:19–28)

34. Stanton K. Sherman. A practical approach to the Echocardiographic evaluation of Ventricular diastolic function. In : Albert C Perrino, Scott T. Reeves (eds), A Practical Approach to Transesophageal Echocardiography, 2nd edition, 2008, Lippincott Williams & Wilkins, Philadelphia, Pg : 146.

35. Sohn D, Chai I, Lee D, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. Journal of American College of Cardiology 1997; 30: 474-480.

CONSENT FORM

Title of the study:

Comparison of the effect of isoflurane and sevoflurane on the left ventricular diastolic function, in patients with ischemic heart disease undergoing coronary artery bypass grafting using cardiopulmonary bypass: An intraoperative transesophageal echocardiographic study.

Study number:

You are being requested to participate in a study to evaluate the effects of the anaesthetic agents - isoflurane and sevoflurane, on the left ventricular diastolic function of the heart with the help of transesophageal echocardiography (TEE). We hope to include about 50 people from this hospital in this study.

What is CABG?

You are going to have a surgery (coronary artery bypass grafting-CABG) on your heart to restore the blood circulation in the blood vessels obstructed due to the ischemic heart disease (IHD).

Why is isoflurane and sevoflurane used for anaesthesia?

Anaesthesia is administered during all surgical procedures so that

- You are asleep during the procedure,
- You are unaware of the procedure, and
- You remain pain free during the surgery.

Isoflurane and Sevoflurane are anaesthetic vapors administered along with oxygen during surgery so that you remain asleep, unaware and pain free. After the procedure, these anesthetic agents are discontinued and you will gradually become awake.

What is transesophageal echocardiography (TEE)?

TEE is ultrasonic equipment useful in monitoring the cardiac function during surgery. The TEE probe is introduced through the

mouth into the esophagus (food pipe of our body) and stomach and the heart is imaged with ultrasound waves. TEE is recommended during all cardiac surgical procedures.

Why are we doing the study?
The heart pumps blood in two phases- systole and diastole. During systole, the heart contracts and during diastole, it relaxes. This study will evaluate the effects of isoflurane and sevoflurane on the relaxation phase (i.e., diastolic function) of the heart.

Is isoflurane and sevoflurane safe to be used for CABG?
The anaesthetic vapors isoflurane and sevoflurane are routinely used during anaesthesia for CABG and are considered safe agents, They cause minimal depression of the heart contractions and helpful in controlling the cardiovascular reflex responses during surgical stress.

What are the side effects of TEE?
TEE may be associated with difficulty in swallowing (1 in 1000), injury to teeth (3 in 1000) and bleeding from stomach (3 in 100000). Rare complications include esophageal perforation and vocal cord paralysis.

Can you withdraw from this study after it starts?
Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?
We do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at no cost to you. We are unable to provide any monetary compensation, however.

Will you have to pay for the study?
No.

Will your personal details be kept confidential?
The results of this study will be published as thesis and in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask

Dr. Soumendu Pal (Tel : 8891780862),
Dr Shrinivas Gadhinglajkar, Additional Professor of Anesthesia, SCTIMST (Tel: 9446304043),
Dr Rupa Sreedhar, Professor of Anesthesia, SCTIMST
(Tel: 9446314043)

or
email: soumendu@sctimst.ac.in

DECLARATION

I, ____ ,

Participant's name: Date of Birth / Age (in years)

Son/daughter of ___________________________________

(Please tick boxes) •

Declare that I have read the above information provide to me regarding the study:

'Comparison of the effect of isoflurane and sevoflurane on the left ventricular diastolic function, in patients with ischemic heart disease undergoing coronary artery bypass grafting using cardiopulmonary bypass: An intraoperative transesophageal echocardiographic study'

And have clarified any doubts that I had. [ ]

• I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

• I also understand that neither I, nor my doctors, will have any choice of whether I will get Isoflurane or Sevoflurane during the conduct of the study. [ ]

• I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]

• I understand that my identity will not be revealed in any information released to third parties or published [ ]

• I voluntarily agree to take part in this study [ ]

• I received a copy of this signed consent form [ ]

Name:

Signature:

Date:
Name of witness:
Relation to participant:
Date:
(Person Obtaining Consent)

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

________________________________ ___________________

Name and Signature of Person Obtaining Consent

<u>**സമ്മതപത്രം**</u>

പഠനപദ്ധതിയുടെ പേര്:

രക്തസഞ്ചാരക്കുറവുമൂലം ഹൃദ്രോഗം വന്നിട്ടുള്ള രോഗികളിൽ, കാർഡിയോപൾമണറി ബൈപാസ്സ് മുഖേന, കൊറോണറി ആർട്ടറി ബൈപാസ്സ് ഗ്രാഫ്റ്റിങ്ങ് എന്ന ഹൃദയ ശസ്ത്രക്രിയ ചെയ്യുമ്പോൾ അവരുടെ ലെഫ്റ്റ് വെൻട്രിക്കുലാർ ഡയസ്റ്റോലിക് ഫങ്ഷനിൽ ഐസോഫ്ളൂറേൻ, സെവോഫ്ളൂറേൻ എന്നീ മയക്കുവാൻ ഉപയോഗിക്കുന്ന മരുന്നുകളുടെ ഉപയോഗം കൊണ്ടുണ്ടാകുന്ന പ്രതിഫലനങ്ങളുടെ ഒരു താരതമ്യപഠം :- ശസ്ത്രക്രിയാ സമയത്ത് അന്നനാളത്തിൽക്കൂടി നടത്തുന്ന എക്കോകാർഡിയോഗ്രാഫിക് പഠനം (TEE).

പഠനത്തിന് വിധേയമാക്കപ്പെടുന്നവരുടെ എണ്ണം:

ഈ പ്രത്യേക ഹൃദയശസ്ത്രക്രിയ സമയത്ത് മയക്കം നൽകുന്നതിന് ആവശ്യമായ ഐസോഫ്ളൂറേൻ, സെവോഫ്ളൂറേൻ എന്നീ മരുന്നുകൾ, നമ്മുടെ ഹൃദയത്തിന്റെ ലെഫ്റ്റ് വെൻട്രിക്കുലാർ ഡയസ്റ്റോളിക് ഫങ്ഷനിൽ വരുത്തുന്ന പ്രതിഫലനങ്ങളെ TEE യുടെ സഹായത്തോടുകൂടി മൂല്യനിർണ്ണയം നടത്താനുള്ള ഒരു പാഠ്യപദ്ധതിയിൽ പങ്കാളിയാകുവാൻ നിങ്ങളോട് വിനീതമായി അഭ്യർത്ഥിക്കുകയാണ്. ഈ ആശുപത്രിയിൽ നിന്നും 50 രോഗികളെ ഉൾപ്പെടുത്തികൊണ്ടുള്ള ഒരു പഠനം നടത്താൻ ഞങ്ങൾ ഉദ്ദേശിക്കുകയാണ്.

CABG എന്നാൽ എന്താണ്?

ഹൃദയ പേശികളിലെ രക്തധമനികളിൽ ഉണ്ടായിരിക്കുന്ന തടസ്സങ്ങളെ മാറ്റി വീണ്ടും രക്തധമനികളിൽ രക്തചംക്രമണം സാധാരണ നിലയിലാക്കുവാനുള്ള ഒരു ഹൃദയശസ്ത്രക്രിയയക്ക് നിങ്ങൾ വിധേയനാകാൻ പോവുകയാണ്. ഇതിനെ കൊറോണറി ആർട്ടറി ബൈപാസ്സ് ഗ്രാഫ്റ്റിങ്ങ് അല്ലെങ്കിൽ CABG എന്ന് പറയുന്നു.

ഐസോഫ്ളൂറേൻ, സെവോഫ്ളൂറേൻ എന്നീ മരുന്നുകൾ മയക്കം നൽകുന്നതിന് ഉപയോഗിക്കുന്നത് എന്തുകൊണ്ടാണ്?

എല്ലാ ശസ്ത്രക്രിയകൾക്കും മരുന്നു നൽകി രോഗികളെ ബോധം കെടുത്താറുണ്ട്. എന്തുകൊണ്ടെന്നാൽ

- ശസ്ത്രക്രിയ സമയത്ത് നിങ്ങൾ ഉറക്കമായിരിക്കും.
- എന്താണ് സംഭവിക്കുന്നത് എന്നതിനെ പറ്റി നിങ്ങൾ ബോധവാനായിരിയ്ക്കു കയില്ല.
- ശസ്ത്രക്രിയ നടക്കുമ്പോൾ നിങ്ങൾക്ക് വേദന അനുഭവപ്പെടുന്നില്ല.

വാതകരൂപത്തിലുള്ള ഐസോഫ്ളൂറേൻ, സെവോഫ്ളൂറേൻ എന്നീ മയക്കാൻ ഉപയോഗിക്കുന്ന മരുന്നുകൾ ഓക്സിജനിൽ കലർത്തി നിങ്ങളുടെ ശ്വാസകോശ ത്തിൽ കടത്തി വിടുമ്പോൾ, നിങ്ങൾ ഉറങ്ങുകയും, വേദന അനുഭവപ്പെടാതിരിക്കുക യും, ചുറ്റുപാടുകളെ പറ്റി ബോധവാനല്ലാതാവുകയും ചെയ്യുന്നു. ശസ്ത്രക്രിയയ്ക്ക് ശേഷം ഈ മരുന്നുകളുടെ ഉപയോഗം നിറുത്തുമ്പോൾ പതുക്കെ നിങ്ങൾ ബോധ വാനാകുന്നു.

TEE എന്നാൽ എന്താണ്?

ഹൃദയ ശസ്ത്രക്രിയ സമയത്ത് ഹൃദയത്തിന്റെ പ്രവർത്തനങ്ങൾ തുടർച്ചയായി നിരീക്ഷിക്കുവാൻ സഹായിക്കുന്ന ഒരു പ്രത്യേക പരിശോധനാരീതിയാണ് ഇത്. TEE ഉപകരണം വായിൽക്കൂടി അന്നനാളത്തിലേക്കും, ആമാശയത്തിലേക്കും കടത്തി, ശബ്ദതരംഗങ്ങൾ വഴി ഹൃദയത്തിന്റെ പ്രവർത്തനങ്ങൾ നിരീക്ഷിക്കുന്നു. TEE എല്ലാ വിധത്തിലുള്ള ഹൃദയശസ്ത്രക്രിയകൾക്കും ഉപയോഗിക്കേണ്ടതാണ്.

ഈ പഠനം നമ്മൾ എന്തിനുവേണ്ടിയാണ് നടത്തുന്നത്?

ചുരുങ്ങുകയും, വികസിക്കുകയും ചെയ്യുന്ന രണ്ടു ഘട്ടങ്ങളിലായിട്ടാണ് മനു ഷ്യഹൃദയം രക്തം പമ്പ് ചെയ്യുന്നത്. ഹൃദയം വികസിക്കുന്ന ഘട്ടത്തിൽ ഐസോ ഫ്ളൂറേൻ, സെവോഫ്ളൂറേൻ എന്നീ മരുന്നുകൾ ഉപയോഗിക്കുമ്പോൾ ഹൃദയത്തിലു ണ്ടാകുന്ന പ്രതിഫലനങ്ങളെ വിലയിരുത്തുന്നതിനുള്ള ഒരു പഠനമാണിത്.

ഐസോഫ്ളൂറേൻ, സെവോഫ്ളൂറേൻ എന്നി മരുന്നുകൾ ഈ ശസ്ത്രക്രിയയ്ക്ക് (CABG) സുരക്ഷിതമായി ഉപയോഗിക്കുവാൻ സാധിക്കുന്നവയാണോ?

വാതകരൂപത്തിലുള്ള ഐസോഫ്ളൂറേൻ, സെവോഫ്ളൂറേൻ എന്നീ മരുന്നു കൾ ഈ ഹൃദയശസ്ത്രക്രിയയ്ക്ക് പതിവായി ഉപയോഗിക്കുന്നതും, സുരക്ഷിതമാ ണെന്ന് കണ്ടിട്ടുള്ളതുമാണ്. ഈ മരുന്നുകൾ നമ്മുടെ ഹൃദയത്തുടിപ്പിൽ വളരെ നേരിയ കുറവ് ഉണ്ടാക്കാൻ സാധ്യതയുണ്ടെങ്കിലും ശസ്ത്രക്രിയമൂലം ഉണ്ടാകുന്ന

കാർഡിയോവാസ്ക്കുലാർ സ്ട്രസ്സ് റെസ്പോൺസസിനെ നിയന്ത്രിക്കുവാൻ വളരെ സഹായിക്കുന്നു.

TEE യുടെ പാർശ്വഫലങ്ങൾ എന്തൊക്കെയാണ്?

TEE ഉപയോഗിക്കുന്നതുകൊണ്ട് വിഴുങ്ങുവാനുള്ള ബുദ്ധിമുട്ട് (1000 പേരിൽ ഒരാൾക്ക്), പല്ലിന് ക്ഷതം (1000 പേരിൽ മൂന്ന് പേർക്ക്) വയറ്റിൽ രക്തസ്രാവം (100,000 പേരിൽ മൂന്ന് പേർക്ക്) എന്നിവ ഉണ്ടാകാം. അപൂർവ്വം ആയിട്ട് കണ്ഠനാളിയ്ക്കും (വോക്കൽകോർട്) അന്നനാളത്തിനും ക്ഷതം ഉണ്ടാകാം.

ഈ പഠനം തുടങ്ങിയതിനുശേഷം ഇതിൽനിന്നും പിന്മാറാൻ നിങ്ങൾക്ക് സാധിക്കുമോ?

നിങ്ങളുടെ തീർത്തും സ്വമേധയാലുള്ള തീരുമാനത്തിലൂടെയാണ് ഈ പഠനത്തിൽ പങ്കുചേരുന്നതും, അതുപോലെ തന്നെ ഇതിൽ താൽപര്യമില്ലെങ്കിൽ നിങ്ങൾക്ക് പിന്മാറാവുന്നതുമാണ്. പിന്മാറിയാലും ഈ ആശുപത്രിയിലെ നിങ്ങളുടെ, പതിവുപോലെയുള്ള ചികിത്സയെ അത് ഒരു വിധത്തിലും ബാധിക്കുകയില്ല.

ഈ പഠനം മൂലം നിങ്ങളുടെ ആരോഗ്യത്തിന് ദോഷകരമായ ഫലങ്ങൾ ഉണ്ടാവുകയാണെങ്കിൽ എന്തുചെയ്യും?

ഈ പഠനം മൂലം നിങ്ങളുടെ ആരോഗ്യത്തിന് യാതൊരു ദോഷഫലങ്ങളും ഉണ്ടാകുമെന്ന് പ്രതീക്ഷിക്കുന്നില്ല. എന്നിരുന്നാലും എന്തെങ്കിലും പാർശ്വഫലങ്ങൾ ഉണ്ടായാൽ അതിനുള്ള ചികിത്സ നിങ്ങൾക്ക് ചിലവുകളൊന്നുമില്ലാതെ തന്നെ ഇവിടെ നൽകുന്നതാണ്. ധനസഹായങ്ങളൊന്നും നൽകാൻ സാധിക്കുകയില്ല.

ഈ പഠനത്തിന് നിങ്ങൾക്ക് എന്തെങ്കിലും ചിലവുകൾ വഹിക്കേണ്ടി വരുമോ?

ഇല്ല

നിങ്ങളുടെ സ്വകാര്യ വിവരങ്ങൾ രഹസ്യമായി സൂക്ഷിക്കുമോ?

ഈ പഠനഫലമായി കിട്ടുന്ന അന്തിമവിവരങ്ങൾ ഒരു പ്രബന്ധമായിട്ടും, അതുപോലെ മെഡിക്കൽ ജേർണലുകളിലും പ്രസിദ്ധീകരിക്കും. എന്നാൽ നിങ്ങളുടെ പേരുവിവരങ്ങളും മറ്റും രഹസ്യമായി തന്നെ സൂക്ഷിക്കും. എങ്കിലും ഈ പഠനവുമായി ബന്ധപ്പെട്ട ആളുകൾക്ക്, നിങ്ങളുടെ രോഗവിവരങ്ങൾ, ഇനി ഒരു സമ്മതം കൂടാതെ തന്നെ പുന:പരിശോധന നടത്താവുന്നതാണ്.

പുതിയതായി നിങ്ങൾക്ക് എന്തെങ്കിലും ചോദിക്കുവാനുണ്ടെങ്കിൽ, താഴെ പറയുന്ന ഡോക്ടർമാരെ സമീപിക്കാവുന്നതാണ്.

ഡോക്ടർ സോമേന്ത്യപാൽ (ഫോൺ നമ്പർ - 8891780862)

ഡോക്ടർ ശ്രീനിവാസ് ഗധിങ്ങ്ലജ്കർ, അനസ്തേഷ്യ വിഭാഗം അഡീഷണൽ പ്രഫസർ, ശ്രീചിത്തിര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഒഫ് മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി (ഫോൺ നമ്പർ 9446304043)

ഡോക്ടർ രൂപ ശ്രീധർ, അനസ്തേഷ്യ വിഭാഗം പ്രഫസർ, ശ്രീചിത്തിര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഒഫ് മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി (ഫോൺ നമ്പർ - 9446314043)

അല്ലെങ്കിൽ

ഇ-മെയിൽ അഡ്രസ്സ് - soumendu@sctimst.ac.in

<u>പ്രഖ്യാപനം</u>

ഞാൻ .... (രോഗിയുടെ പേര്)

.... (ജനനതീയതി) .... (വയസ്സ്

വർഷങ്ങളിൽ) .... യുടെ പുത്രൻ /പുത്രി

(താഴെകാണുന്ന ബ്രാക്കറ്റുകളിൽ ✓ അടയാളം ഇടുക)

ഈ പ്രത്യേക പഠനത്തെക്കുറിച്ച് മുകളിൽ പറഞ്ഞിരിക്കുന്ന വിശദവിവരങ്ങൾ വായിച്ച് മനസ്സിലാക്കിയതായി പ്രഖ്യാപിക്കുന്നു.

''രക്തസഞ്ചാരക്കുറവുമൂലം ഹൃദ്രോഗം വന്നിട്ടുള്ള രോഗികളിൽ, കാർഡിയോ പൾമണറി ബൈപാസ്സ് മുഖേന, കൊറോണറി ആർട്ടറി ബൈപാസ്സ് ഗ്രാഫ്റ്റിങ്ങ് എന്ന ഹൃദയ ശസ്ത്രക്രിയ ചെയ്യുമ്പോൾ അവരുടെ ലെഫ്റ്റ് വെൻട്രിക്കുലാർ ഡയസ്റ്റോളിക് ഫങ്ക്ഷനിൽ, ഐസോഫ്ളൂറേൻ, സെവോഫ്ളൂറേൻ എന്നീ മയക്കു മരുന്നുകളുടെ ഉപയോഗം കൊണ്ടുണ്ടാകുന്ന പ്രതിഫലനങ്ങളുടെ ഒരു താരതമ്യപഠനം : ശസ്ത്ര ക്രിയാ സമയത്ത് അന്നനാളത്തിൽക്കൂടി നടത്തുന്ന ഒരു എക്കോകാർഡിയോഗ്രാഫിക് പഠനം (TEE)''.

എനിക്കുണ്ടായിരുന്ന എല്ലാ സംശയങ്ങളും ചോദിച്ചു മനസ്സിലാക്കിയിട്ടുണ്ട് (   )

- ഈ പഠനത്തിലുള്ള എന്റെ പങ്കാളിത്തം തികച്ചും എന്റെ സ്വമനസ്സാലെയുള്ള തീരുമാനമാണെന്നും, എന്റെ ചികിത്സയെ പ്രതികൂലമായി ബാധിക്കാതെയും, എന്റെ നിയമപരമായ ആവശ്യങ്ങൾക്ക് കോട്ടം തട്ടാതെയും, എപ്പോൾ വേണ മെങ്കിലും എനിക്ക് ഇതിൽ നിന്നും പിന്മാറാൻ സാധിക്കുമെന്നും ഞാൻ മനസ്സി ലാക്കുന്നു (   )

- ഈ പഠനം നടക്കുന്ന സമയത്ത് എനിക്ക് ഐസോഫ്ളൂറേൻ എന്ന മരുന്നു ആണോ, അതോ സെവോഫ്ളൂറേൻ എന്ന മരുന്ന് ആണോ ലഭിക്കുന്നതെന്ന് തിരഞ്ഞെടുക്കുവാൻ ഉള്ള അവകാശം, എനിക്കോ എന്റെ ഡോക്ടർമാർക്കോ ഇല്ല എന്നുള്ളതും ഞാൻ മനസ്സിലാക്കുന്നു (   )

- ഈ പാഠ്യപദ്ധതിയിൽ നിന്ന് പിന്മാറിയാലും, എന്റെ അനുവാദമില്ലാതെ തന്നെ, ഈ പഠനം നടത്തുന്ന ഡോക്ടർമാർക്കും, ഈ സ്ഥാപനത്തിലെ എത്തിക്കൽ കമ്മിറ്റി അംഗങ്ങൾക്കും എന്റെ രോഗവിവരരേഖകൾ പരിശോധിക്കാവുന്നതാണെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. ഇതിന് എനിക്ക് സമ്മതാണ് (   )

- എന്നെക്കുറിച്ചുള്ള വിശദവിവരങ്ങൾ പരസ്യപ്പെടുത്തുകയോ, മൂന്നാമതൊരാ ളിന് കൈമാറുകയോ ചെയ്യുന്നില്ലെന്നുള്ള വസ്തുതയും ഞാൻ മനസ്സിലാ ക്കുന്നു (   )

- ഈ പാഠ്യപദ്ധതിയിൽ പങ്കുചേരുന്നതിന് ഞാൻ സ്വമനസ്സാലെ സമ്മതിച്ചിരി ക്കുന്നു (   )

- ഈ സമ്മതപത്രത്തിന്റെ കയ്യൊപ്പുള്ള ഒരു പകർപ്പ് ഞാൻ കൈപ്പറ്റിയിരി ക്കുന്നു (   )

പേര് :

ഒപ്പ് :

തീയതി :

സാക്ഷി :

രോഗിയുമായുള്ള ബന്ധം

തീയതി :

(സമ്മതം വാങ്ങുന്ന വ്യക്തി)

ഈ പ്രത്യേക വൈദ്യശാസ്ത്രപഠന പദ്ധതിക്കുവേണ്ടിയുള്ള സമ്മതപത്രത്തിന് ആവശ്യമായ എല്ലാവിവരങ്ങളും വളരെ തൃപ്തികരമായ രീതിയിൽ ഇതിൽ അടങ്ങിയിട്ടുണ്ടെന്ന് ഞാൻ സാക്ഷ്യപ്പെടുത്തിക്കൊള്ളുന്നു. ഇതിൽ പങ്കാളികളായ രോഗികളോട് ഈ പഠനത്തെപ്പറ്റി വിശദമായി സംസാരിക്കുകയും, ഈ സമ്മതപത്രത്തിൽ അടങ്ങിയിരിക്കുന്ന വിവരങ്ങൾ സാധാരണ സംസാരഭാഷയിൽ തന്നെ പറഞ്ഞു മനസ്സിലാക്കുകയും ചെയ്തിട്ടുണ്ട്. ഇതിനിടയിൽ ഉണ്ടായേക്കാവുന്ന അപകട സാധ്യതകളെയും, പ്രതികൂലഫലങ്ങളെയും കുറിച്ച് വിശദമായി പറഞ്ഞ് മനസ്സിലാക്കിയിട്ടുണ്ട്. ഇതിനെപ്പറ്റിയുള്ള കൂടുതൽ വിവരങ്ങൾ ചോദിക്കുവാൻ ഈ രോഗികളെ പ്രോത്സാഹിപ്പിക്കുകയും, എല്ലാ ചോദ്യങ്ങൾക്കും വ്യക്തമായ മറുപടി നൽകുകയും ചെയ്തിട്ടുണ്ടെന്ന് ഇതിനാൽ ബോധ്യപ്പെടുത്തുന്നു.

സമ്മതം വാങ്ങുന്ന വ്യക്തിയുടെ

പേര് :

ഒപ്പ് :

COMPARISON OF EFFECT OF ISOFLURANE AND SEVOFLURANE ON LEFT VENTRICULAR DIASTOLIC FUNCTION, IN PATIENTS WITH ISCHEMIC HEART DISEASE UNDERGOING CORONARY ARTERY BYPASS GRAFTING USING CARDIOPULMONARY BYPASS: AN INTRAOPERATIVE TRANSESOPHAGEAL ECHOCARDIOGRAPHIC STUDY.

Name of the patient:
Age:
Sex:
Hospital number:
Diagnosis and surgery:

Weight (kg):
Height (cm):
Body surface area (kg/ cm2):
Date of surgery:

RISK FACTORS:

Hypertension	
DM	
Smoking	
COPD / Lung Disease	
Renal / Hepatic Dysfunction	
Dyslipidemia	
LVEF	
Others	
Pre-Op Cardiac Drugs	

HEMODYNAMIC PARAMETERS:

TIME(mins)	0 min	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min
HR													
SBP													
DBP													
MBP													
CVP													
SpO2													
BIS													

TEE PARAMETERS:

TEE MEASUREMENTS	BASELINE	STUDY PERIOD
E (cm/s)		
A (cm/s)		
E / A ratio		
DT (ms)		
A duration (ms)		
S (cm/s)		
D (cm/s)		
S / D ratio		
Ar (cm/s)		
Ar duration (ms)		
e’ (cm/s)		
a’ (cm/s)		
e’/a’ ratio		
IVRT(TDI) (ms)		
E/e’ ratio		

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौघोगिकी संस्थान
तिरुवनन्तपुरम - 695 011, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM - 695 011, INDIA
(An Institute of National Importance under Govt. of India)

Institutional Ethics Committee (IEC)

SCT / IEC-364/ MAY-2011

08-06-2011

Dr. Soumendu Pal
Resident, DM (Anaesthesiology)
SCTIMST.

Dear Dr. Soumendu Pal,

The Institutional Ethics Committee reviewed and discussed your application to conduct the clinical trial entitled "Comparison of Effect of Isoflurane and Sevoflurane on Left Ventricular Diastolic Function, in Patients with Ischemic Heart Disease Undergoing Coronary Artery Bypass Grafting Using Cardiopulmonary Bypass: An Intraoperative Transesophageal Echocardiographic Study"

The following documents were reviewed:

1. *Covering letter dated 28/2/2011.*
2. *Study Proposal.*
3. *Technical Advisory Committee (TAC) permission.*
4. *Technical Advisory Committee (TAC) form.*
5. *Institutional Ethics Committee (IEC) form.*
6. *Observation Chart.*
7. *Consent form (English).*
8. *Consent form (Malayalam).*
9. *CV of Investigators.*
10. *Declaration form.*

तार : चित्रमेट
Grams : Chitramet
फोन
Phone : 2443152
फाक्स
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2550728
ई-मेइल
E-mail : sct.@sctimst.ker.nic.in

The following members of the Ethics committee were present at the meeting held on 28th May, 2011 at Director's Conference Hall.

Sl. No	Member Name	Highest Degree	Gender	Scientific / Non-scientific	Affiliation with Institution (s)
1.	Justice M.R. Hariharan Nair.	MA BL	Male	Legal Expert (Chairperson)	No
2.	Prof. K. Radhakrishnan	MD	Male	Clinician (Neurologist)	Yes
3.	Dr. G. S. Bhuvaneshwar	PhD	Male	Basic Scientist (Biomedical Expert)	Yes
4.	Smt. Lalithambika IAS	MBA	Female	Lay Person (Administrator)	No
5.	Dr. Rema M. N	MD	Female	Pharmacologist	No
6.	Dr. P. G. Premila	MD	Female	Clinician (Paediatrician)	No
7.	Dr. Meenu Hariharan	DM	Female	Clinician (Gastro Enterologist)	No
8.	Dr. Girish Menon	MCh	Male	Neurosurgeon/Ethicist	Yes
9.	Dr. Anoopkumar Thekkuveettil	PhD	Male	Basic Scientist (Molecular Biology) /Ethicist (Member Secretary)	Yes

IEC Decision

Approved the trial to be conducted in its present form

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Yours Sincerely

Dr. Anoopkumar Thekkuveettil
Member Secretary, Ethics Committee.

LIST OF ABBREVIATIONS

CHF: Congestive heart failure

IHD: Ischemic heart disease

RWMA: Regional wall motion abnormalities

CPB: Cardiopulmonary bypass

LV: Left ventricle

TEE: Transesophageal Echocardiography

LA: Left atrium

MV: Mitral valve

TMBF: Transmitral blood flow

PV: Pulmonary vein

TDI: Tissue Doppler Imaging

PWD: Pulse Wave Doppler.

ms: milliseconds

CAD: Coronary artery disease

BIS: Bispectral Index

OPD: Out Patient Department.

MASTER CHART

ISOFLURANE GROUP

(1) PATIENT PARTICULARS.

SL.NO.	Name	Age	Sex	ID	Weight	LVEF
1	PKN	49	M	324369	64	68
2	CHN	56	F	325109	68	70
3	SH	60	M	317210	56	78
4	VVK	70	M	324658	61	76
5	PUS	64	M	331168	72	65
6	JM	60	M	332408	77	58
7	KPN	62	M	328122	62	76
8	SOM	55	M	319097	67	58
9	SVK	58	F	332194	54	67
10	BHR	56	F	354674	61	64
11	CGN	68	M	312896	49	61
12	SUD	58	M	319251	79	65
13	VAS	45	F	330017	44	72
14	SHK	56	M	332479	56	73
15	HKT	52	M	336097	81	67
16	MDH	56	M	340848	65	58
17	CLM	52	M	334044	74	61
18	SDN	56	M	332700	56	69
19	VLU	62	M	329148	62	75
20	ABG	61	M	336681	61	72
21	SRT	52	F	334410	65	64
22	RJM	55	F	181590	73	65
23	LKM	59	F	338850	63	72
24	MAN	62	M	314557	56	66
25	DKS	56	F	378521	60	68

(2) CHANGES IN HEART RATE (HR) AT VARIOUS TIME POINTS (MINS)

SL.NO.	HR0	HR5	HR10	HR15	HR20	HR25	HR30	HR35
1	71	68	67	70	76	72	70	74
2	76	78	78	80	72	74	68	70
3	66	68	70	68	66	67	70	74
4	77	79	80	82	78	76	78	80
5	57	58	60	56	52	54	60	62
6	80	82	78	80	84	86	82	80
7	80	82	84	80	78	80	83	84
8	62	60	65	66	68	70	68	62
9	62	60	61	61	60	64	66	63
10	45	46	44	48	50	54	50	48
11	55	58	56	58	60	62	56	54
12	53	50	48	50	56	58	60	62

13	80	78	76	80	82	84	85	84
14	60	68	66	64	60	62	62	62
15	58	60	60	64	64	62	60	62
16	53	54	55	53	56	54	55	56
17	58	60	60	58	59	60	54	56
18	84	84	82	78	79	80	84	82
19	76	76	78	80	82	80	78	78
20	83	82	82	80	78	76	80	80
21	50	50	54	56	60	58	56	58
22	48	50	52	54	50	54	52	56
23	67	68	68	69	70	72	74	70
24	64	64	68	63	66	69	62	68
25	78	76	75	77	75	77	78	76

(3) CHANGES IN SYSTOLIC BLOOD PRESSURE (SBP) AT VARIOUS TIME POINTS (MINS)

SL NO.	SBP0	SBP5	SBP10	SBP15	SBP20	SBP25	SBP30	SBP35
1	140	138	148	136	136	140	142	148
2	126	128	130	128	124	110	112	108
3	168	164	162	154	152	150	156	154
4	164	162	160	158	162	156	150	148
5	134	136	130	128	124	112	126	130
6	132	132	138	140	142	142	146	150
7	112	110	126	124	116	118	124	121
8	178	174	114	156	158	160	152	148
9	153	156	146	142	140	152	150	156
10	124	128	130	116	112	110	108	110
11	98	112	108	110	124	118	115	112
12	142	147	139	145	142	141	140	148
13	132	130	126	121	130	126	124	139
14	130	136	90	132	138	142	137	140
15	140	158	142	148	150	154	168	158
16	164	125	142	146	138	139	144	142
17	125	130	132	134	142	146	148	150
18	132	112	110	136	134	132	148	144
19	130	128	126	124	125	132	132	136
20	142	138	142	144	148	146	150	148
21	156	160	139	142	147	138	132	130
22	112	126	119	125	124	113	110	108
23	129	125	127	123	126	128	130	138
24	126	135	136	145	142	148	142	150
25	154	152	154	143	146	153	158	153

(4) CHANGES IN DIASTOLIC BLOOD PRESSURE (DBP) AT VARIOUS TIME POINTS (MINS)

SL NO.	DBP0	DBP5	DBP10	DBP15	DBP20	DBP25	DBP30	DBP35
1	89	88	90	90	86	86	88	90
2	68	66	68	70	68	60	60	58
3	100	98	96	96	94	98	96	96
4	102	100	98	96	92	90	92	90
5	68	66	68	66	64	56	68	70
6	68	66	64	66	64	60	58	60
7	60	58	56	58	60	62	64	68
8	110	108	60	96	90	98	96	92
9	96	98	94	90	88	89	89	90
10	60	56	58	56	54	56	60	58
11	56	60	56	58	64	58	60	60
12	78	83	76	79	80	82	74	72
13	80	78	72	76	78	80	82	80
14	96	98	52	90	96	92	89	90
15	80	89	86	89	90	94	100	98
16	109	89	90	92	89	88	86	86
17	78	80	80	81	89	90	90	96
18	90	60	60	72	78	80	82	78
19	80	78	78	80	76	80	78	78
20	80	78	80	90	87	88	80	78
21	96	98	88	89	90	90	88	90
22	67	78	68	66	66	68	60	60
23	65	66	65	64	67	63	67	70
24	86	85	83	87	85	88	86	90
25	90	92	88	87	86	87	89	90

(5) CHANGES IN MEAN BLOOD PRESSURE (MBP) AT VARIOUS TIME POINTS (MINS)

SL NO.	MAP0	MAP5	MAP10	MAP15	MAP20	MAP25	MAP30	MAP35
1	106	105	109	105	103	104	106	109
2	87	87	89	89	87	77	77	75
3	123	120	118	115	113	115	116	115
4	123	121	119	117	115	112	111	109
5	90	89	89	87	84	75	87	90
6	89	88	89	91	90	87	87	90
7	77	75	79	80	79	81	84	86
8	133	130	78	116	113	119	115	111
9	115	117	111	107	105	110	109	112
10	81	80	82	76	73	74	76	75
11	70	77	73	75	84	78	78	77
12	99	104	97	101	101	102	96	97
13	97	95	90	91	95	95	96	100
14	107	111	65	104	110	109	105	107
15	100	112	105	109	110	114	123	118

16	127	101	107	110	105	105	105	105
17	94	97	97	99	107	109	109	114
18	104	77	77	93	97	97	104	100
19	97	95	94	95	92	97	96	97
20	101	98	101	108	107	107	103	101
21	116	119	105	107	109	106	103	103
22	82	94	85	86	85	83	77	76
23	86	86	86	84	87	85	88	93
24	99	102	101	106	104	108	105	110
25	111	112	110	106	106	109	112	111

(6) CHANGES IN CENTRAL VENOUS PRESSURE (CVP) AT VARIOUS TIME POINTS (MINS)

SL NO.	CVP0	CVP5	CVP10	CVP15	CVP20	CVP25	CVP30	CVP35
1	6	6	6	8	8	6	8	7
2	8	8	8	7	7	6	5	6
3	10	10	11	12	12	10	10	9
4	9	8	12	12	11	10	11	11
5	8	8	9	9	10	8	8	7
6	5	5	6	7	7	7	6	6
7	5	7	7	6	6	7	7	8
8	8	8	9	10	9	9	8	8
9	11	12	12	11	12	11	12	11
10	9	9	9	10	10	12	11	12
11	8	7	7	7	8	8	7	7
12	4	6	6	5	6	6	6	6
13	6	5	6	6	7	7	7	8
14	6	6	6	5	6	6	5	6
15	10	9	9	9	10	9	8	8
16	9	8	8	9	8	8	8	9
17	11	9	9	9	8	8	5	6
18	8	9	9	10	9	9	9	8
19	13	13	12	10	10	10	10	10
20	6	7	7	6	7	7	6	6
21	4	4	6	5	6	6	6	6
22	6	7	8	8	8	7	7	8
23	5	5	5	6	6	6	5	6
24	6	6	8	8	7	6	6	5
25	6	7	7	7	7	8	7	7

(7) CHANGES IN OXYGEN SATURATION (SpO2) AT VARIOUS TIME POINTS (MINS)

SL NO.	SpO2_0	SpO2_5	SpO2_10	SpO_15	SpO2_20	SpO_25	SpO2_30	SpO2_35
1	99	100	100	98	100	99	100	100
2	100	100	100	99	100	100	98	100
3	100	100	99	100	100	100	100	99
4	100	100	100	100	100	100	100	100
5	100	100	99	100	99	100	100	100
6	100	100	100	100	100	100	100	100
7	100	99	100	100	100	99	100	100
8	98	100	99	100	100	98	100	100
9	100	100	100	100	100	98	100	100
10	100	98	100	100	100	100	100	100
11	100	100	100	100	100	100	100	100
12	100	98	100	99	100	100	98	100
13	100	100	100	100	100	100	98	100
14	100	100	100	100	100	100	100	100
15	100	99	100	98	100	100	100	100
16	100	100	100	100	100	100	100	100
17	100	100	100	100	100	100	100	100
18	99	100	100	99	100	100	100	100
19	100	99	100	100	98	100	99	100
20	100	100	100	100	100	100	100	100
21	100	100	100	100	100	100	99	100
22	100	100	100	98	100	100	100	99
23	100	99	100	98	100	100	100	100
24	100	100	99	99	99	98	99	99
25	100	100	100	100	100	100	100	100

(8) CHANGES IN BISPECTRAL INDEX (BIS) AT VARIOUS TIME POINTS (MINS)

SL NO.	BIS_0	BIS_5	BIS_10	BIS_15	BIS_20	BIS_25	BIS_30	BIS_35
1	45	46	48	50	52	49	48	47
2	62	56	56	52	51	50	45	46
3	54	56	59	60	62	58	48	44
4	42	45	44	43	44	45	48	50
5	54	55	54	51	46	54	56	52
6	37	39	40	38	45	44	42	40
7	56	53	57	53	53	53	55	56
8	58	62	54	50	56	54	53	55
9	48	49	47	48	46	50	49	47
10	38	36	40	42	43	42	39	43
11	56	57	59	54	56	57	58	60
12	52	53	51	40	45	44	42	47
13	48	46	45	46	44	46	44	42
14	46	44	46	47	46	44	45	43
15	54	53	52	50	48	47	48	49

16	46	47	49	50	51	53	49	50
17	59	57	54	52	49	48	47	44
18	56	51	53	55	51	49	47	45
19	64	62	57	55	51	50	54	52
20	53	51	50	49	45	44	44	42
21	54	55	45	44	46	49	51	56
22	62	59	60	47	49	44	47	48
23	56	58	56	55	51	54	60	58
24	62	54	53	54	56	55	53	54
25	56	55	53	50	53	56	54	51

(9) TEE TRANSMITRAL BLOOD FLOW PARAMETERS (CONTROL)

SL NO.	E_Vmax_1	A_Vmax_1	E/A	DT_1	A_duration_1
1	38	55.1	0.69	248	140
2	43.4	59.8	0.72	268	123
3	31.5	34.2	0.92	222	180
4	57.3	75.6	0.75	262	140
5	60.9	54.3	1.12	194	140
6	40.7	57	0.7	280	171
7	42.1	51.6	0.81	190	141
8	38.5	47.6	0.8	208	154
9	56.6	64.4	0.87	261	166
10	63.2	41.5	1.52	208	180
11	55.5	56.9	0.97	190	166
12	35.3	68	0.51	243	130
13	39.1	54.2	0.72	225	125
14	40.3	48.8	0.82	187	127
15	71.6	39.1	1.83	176	119
16	64.8	62.3	1.03	183	160
17	42.6	79.5	0.53	246	148
18	55.9	48.5	1.15	193	121
19	34	39	0.87	204	165
20	31.3	41.2	0.75	299	158
21	65.1	63.6	1.03	229	183
22	67.5	36.5	1.84	158	137
23	59.3	69	0.85	236	141
24	52.4	54.6	0.97	228	136
25	64	53	1.2	210	156

(10) TEE PULMONARY VENOUS BLOOD FLOW PARAMETERS (CONTROL)

SL NO.	S_vmax_1	D_vmax_1	S/D_1	Ar_vmax_1	Ar_vmax_dur_1	A-AR 1
1	51.8	26.5	1.95	18.5	85	55.00
2	23.4	14.1	1.65	10.3	85	38.00
3	20.88	15.08	1.33	10.6	116	64.00
4	39.82	18.1	2.2	10.4	63	77.00
5	37.1	18.6	1.99	13.4	103	37.00
6	34.2	22.5	1.52	18.2	130	41.00
7	57.6	31.9	1.8	15.5	77	64.00
8	44.8	28.8	1.55	12	74	80.00
9	42.1	27.7	1.51	15.7	81	85.00
10	40.9	30.7	1.33	10.8	123	57.00
11	33.5	26.4	1.26	9.6	105	61.00
12	34.7	20.2	1.7	16.9	92	38.00
13	37.9	18.1	2.09	9.63	60	65.00
14	39.6	23.7	1.7	25.1	108	19.00
15	42.1	39.1	1.07	10.2	98	21.00
16	30	15.4	1.9	13.1	127	33.00
17	25.5	15.9	1.6	23.1	103	45.00
18	35.4	27	1.31	22.3	119	2.00
19	38.9	26.6	1.46	18.5	82	83.00
20	35.2	19.3	1.84	9.63	99	59.00
21	35.7	26.7	1.33	7.74	77	106.00
22	33.5	11.2	2.9	8.6	113	24.00
23	36.2	18.9	1.9	11.2	116	25.00
24	32.7	20.9	1.5	10.5	115	21.00
25	36	26	1.4	9	127	29.00

(11) TEE TISSUE DOPPLER IMAGING PARAMETERS (CONTROL)

SL NO.	E1_1	A1_1	E1/A1_1	IVRT_1	E_1/E1_1
1	8.8	13.2	0.8	111	4.32
2	3.73	7.68	0.48	116	11.64
3	4.72	5.13	0.93	204	6.67
4	4.98	14.1	0.35	77	11.51
5	10.7	12.1	0.88	88	5.69
6	6.95	6.43	1.03	148	5.86
7	8.3	9.02	0.92	95	5.07
8	6.95	10.3	0.7	109	5.54
9	5.39	8.5	0.63	141	10.50
10	7.36	4.77	1.54	180	8.59
11	6.33	7.99	0.79	169	8.77
12	6.53	13.3	0.48	86	5.41
13	4.77	7.54	0.63	137	8.20
14	5.29	8.82	0.6	180	7.62
15	7	2.94	2.38	108	10.23

16	5.91	4.77	1.2	139	10.96
17	5.29	11.8	0.44	106	8.05
18	8.08	8.18	1	114	6.92
19	5.19	6.57	0.76	124	6.55
20	9.02	11.9	0.81	141	3.47
21	5.2	5.5	0.94	85	12.52
22	11.9	7.47	1.6	144	5.67
23	6.05	7.8	0.76	116	9.80
24	8.2	7.4	1.1	107	6.39
25	8	7	1.14	124	8.00

(12) TEE TRANSMITRAL BLOOD FLOW PARAMETERS (STUDY)

SL NO.	E_Vmax_2	A_Vmax_2	E_2/A_2	DT_2	A_duration_2
1	53.5	52.5	1.01	211	132
2	49.5	60.2	0.82	231	104
3	42.4	29.9	1.41	183	165
4	50	63.6	0.62	210	154
5	51.3	61.2	0.83	210	119
6	57.8	55.6	1.03	236	160
7	54.6	68.4	0.79	296	130
8	51.3	51.9	0.98	176	162
9	77.8	76.3	1.01	211	154.9
10	53	47.6	1.11	180	154
11	55.9	56.6	1	173	144
12	42.4	58.3	0.7	180	151
13	57.8	79.7	0.72	173	90
14	62.1	50.1	1.23	172	179.6
15	73.4	45.1	1.62	166	124
16	60.3	46	1.7	187	200
17	43.3	53	0.81	204	172
18	44.3	50.7	0.88	187	103
19	50	36.6	1.36	180	132
20	45.4	36.7	1.23	240	148
21	67.7	45.6	1.5	232	176
22	49	34.8	1.4	187	102
23	76.4	50.6	1.5	194	141
24	56.8	48.2	1.18	189	140
25	60.5	54.5	1.1	196	152

(13) TEE PULMONARY VENOUS BLOOD FLOW PARAMETERS (STUDY)

SL NO.	S_vmax_2	D_vmax_2	S/D_2	Arvmax_2	Arvmax_dur_2	A-Ar 2
1	59.65	35.5	1.68	14.1	63.5	69
2	24.1	15.1	1.59	9.3	95	9
3	22.9	31.3	0.73	10.8	127	38
4	42	25.1	1.68	16.4	60	94
5	59.2	22.6	2.61	14.9	106	13
6	31	26.8	1.2	18.7	106	54
7	25.9	23.2	1.11	19.6	74	56
8	47.8	27.9	1.7	9.63	63	99
9	50.5	38.9	1.29	14.6	95	60
10	37.6	28.2	1.33	9.4	93	61
11	22.2	17.6	1.3	6.02	77	67
12	32.7	20.8	1.6	11.9	95	56
13	52.4	28.3	1.85	12	67	23
14	42.9	25	1.71	21.7	109	71
15	23.1	30.8	0.74	9.63	103	21
16	24.1	35.6	0.7	25	137	63
17	39.5	30.3	1.31	135	81	91
18	28.9	12	2.15	13.8	70	33
19	44.8	34	1.31	10.8	85	47
20	23	18.4	1.3	7.8	148	0
21	34.8	30	1.16	9.1	102	74
22	52.5	15.5	3.4	7.74	85	17
23	47.5	42.8	1.1	21.4	134	7
24	30.7	24.3	1.27	9.7	110	30
25	30.6	22.9	1.36	11.2	110	42

(14) TEE TISSUE DOPPLER IMAGING PARAMETERS (STUDY)

SL NO.	E1_2	A1_2	E1/A1_2	IVRT_2	E_2/E1_2
1	9.85	12.4	0.8	105	5.43
2	4.87	9.4	0.51	95	10.16
3	6.12	3.55	1.7	167	6.93
4	5.19	10.7	0.48	123	9.63
5	7.3	10.95	0.66	102	7.03
6	4.98	7.26	0.68	181	11.61
7	7.05	5.6	1.25	116	7.74
8	8.3	8.4	0.98	106	6.18
9	6.31	8.24	0.76	106	12.33
10	5.5	7.68	0.71	144	9.64
11	5.7	5.5	1.03	155	9.81
12	6.22	10.6	0.6	116	6.82
13	5.57	9.01	0.61	102	10.38
14	7.05	11	0.64	125	8.81
15	5.96	3.46	1.72	114	12.32
16	4.46	5.91	0.8	106	13.52

17	3.73	7.78	0.48	116	11.61
18	7.87	10.6	0.74	85	5.63
19	5.7	8.3	0.68	111	8.77
20	11.5	8.4	1.4	109	3.95
21	5.45	4.72	1.15	92	12.42
22	11.3	5.5	2	88	4.34
23	8.65	5.32	1.62	141	8.83
24	7.8	6.9	1.13	114	7.28
25	7.8	6.5	1.2	121	7.76

SEVOFLURANE GROUP

(15) PATIENT PARTICULARS

SL NO.	Name	Age	Sex	ID	Weight	LVEF
1	KNK	50	M	320953	64	72
2	JPN	54	M	321787	68	64
3	JNT	46	F	324146	56	76
4	VPN	69	M	326605	61	58
5	TP	50	M	331406	72	71
6	RDH	73	F	305502	77	82
7	LMY	65	F	325525	64	67
8	PDM	65	F	334055	67	63
9	RSD	61	M	202885	54	68
10	PLN	54	M	321986	61	61
11	SRK	45	M	339288	49	72
12	GPN	57	M	336551	79	58
13	JDN	62	M	342393	44	75
14	GP	61	F	275084	56	56
15	DRH	74	M	7816	81	83
16	ADT	64	F	324051	53	58
17	GMT	64	F	333904	42	64
18	HAM	56	M	306719	74	62
19	PLY	58	M	326826	79	72
20	ARD	61	M	235527	58	76
21	ANT	62	F	341995	66	75
22	PIR	57	F	324558	73	78
23	SHJ	63	M	354551	56	58
24	PKS	65	M	366793	49	65
25	RVT	69	F	347882	72	76

(16) CHANGES IN HEART RATE (HR) AT VARIOUS TIME POINTS (MINS)

SL NO.	HR0	HR5	HR10	HR15	HR20	HR25	HR30	HR35
1	68	70	64	66	68	76	64	66
2	67	68	70	72	72	68	68	65
3	53	54	53	55	56	54	54	62
4	71	71	70	72	76	72	71	76
5	78	76	78	77	78	78	80	80
6	77	78	80	77	76	78	80	80
7	60	62	64	60	62	58	60	60
8	50	53	52	53	52	56	54	50
9	70	69	70	71	74	68	70	71
10	49	48	50	48	49	49	48	50
11	48	46	48	46	46	47	48	49
12	64	66	64	65	64	62	65	64
13	61	60	60	60	62	61	62	60
14	74	76	73	70	71	73	74	74
15	88	86	86	84	88	89	88	96
16	61	60	62	62	62	61	60	61
17	81	83	84	86	83	84	84	87
18	78	80	81	80	82	83	82	84
19	75	76	75	73	74	74	75	78
20	38	40	40	42	38	39	40	38
21	68	68	64	63	65	66	68	65
22	76	76	74	72	74	68	65	66
23	56	65	66	68	70	73	75	65
24	54	55	56	54	55	54	55	53
25	76	77	78	76	75	74	78	78

(17) CHANGES IN SYSTOLIC BLOOD PRESSURE (SBP) AT VARIOUS TIME POINTS (MINS)

SL NO.	SBP0	SBP5	SBP10	SBP15	SBP20	SBP25	SBP30	SBP35
1	134	122	146	132	110	90	124	150
2	130	138	138	132	136	136	138	87
3	142	144	142	142	140	139	145	146
4	124	125	128	130	125	127	125	123
5	145	142	142	145	144	146	144	142
6	156	154	147	142	120	110	96	96
7	134	136	132	134	135	133	130	132
8	143	144	141	142	142	138	139	140
9	123	122	120	124	122	124	128	130
10	157	165	156	149	150	152	160	162
11	129	156	153	148	145	144	138	132
12	160	162	148	154	168	162	158	153
13	120	124	126	124	123	121	120	125
14	156	149	147	145	150	151	154	152
15	137	139	140	146	139	137	139	140
16	145	144	142	141	144	142	142	145
17	121	116	113	112	121	120	110	112
18	156	152	152	153	157	158	152	150

19	188	163	162	152	150	154	158	152
20	148	150	151	152	153	149	150	152
21	124	125	122	127	134	132	134	140
22	154	153	152	142	146	146	143	146
23	154	156	154	152	157	154	153	90
24	162	143	153	142	154	134	143	144
25	134	132	132	136	134	135	138	132

(18) CHANGES IN DIASTOLIC BLOOD PRESSURE (DBP) AT VARIOUS TIME POINTS (MINS)

SL NO.	DBP0	DBP5	DBP10	DBP15	DBP20	DBP25	DBP30	DBP35
1	90	86	84	86	90	68	86	96
2	86	87	88	86	88	86	84	86
3	78	70	76	75	78	80	82	78
4	80	82	78	80	81	80	80	78
5	82	80	81	80	81	80	78	78
6	90	98	90	96	80	72	70	60
7	87	88	87	88	88	89	86	87
8	80	78	78	77	78	78	77	78
9	68	66	68	65	67	66	66	64
10	90	92	92	89	93	92	89	89
11	80	89	88	87	88	82	80	78
12	96	89	87	90	88	92	96	96
13	72	70	70	68	70	72	71	70
14	87	86	88	87	89	87	88	87
15	80	78	77	78	80	80	87	80
16	86	86	85	87	85	83	82	84
17	66	60	68	66	58	60	68	66
18	90	90	91	90	92	90	89	88
19	96	98	100	98	92	91	82	98
20	88	89	90	89	87	88	89	90
21	68	74	68	64	64	67	75	74
22	90	88	88	88	86	84	86	83
23	90	98	96	90	91	92	89	88
24	98	90	88	89	88	86	89	86
25	78	76	76	77	76	75	72	72

(19) CHANGES IN MEAN BLOOD PRESSURE (MBP) AT VARIOUS TIME POINTS (MINS)

SL NO.	MAP0	MAP5	MAP10	MAP15	MAP20	MAP25	MAP30	MAP35
1	105	98	105	101	97	75	99	114
2	101	104	105	101	104	103	102	86
3	99	95	98	97	99	100	103	101
4	95	96	95	97	96	96	95	93
5	103	101	101	102	102	102	100	99
6	112	117	109	111	93	85	79	72
7	103	104	102	103	104	104	101	102
8	101	100	99	99	99	98	98	99
9	86	85	85	85	85	85	87	86
10	112	116	113	109	112	112	113	113
11	96	111	110	107	107	103	99	96
12	117	113	107	111	115	115	117	115
13	88	88	89	87	88	88	87	88
14	110	107	108	106	109	108	110	109
15	99	98	98	101	100	99	104	100
16	106	105	104	105	105	103	102	104
17	84	79	83	81	79	80	82	81
18	112	111	111	111	114	113	110	109
19	127	120	121	116	111	112	107	116
20	108	109	110	110	109	108	109	111
21	87	91	86	85	87	89	95	96
22	111	110	109	106	106	105	105	104
23	111	117	115	111	113	113	110	89
24	119	108	110	107	110	102	107	105
25	97	95	95	97	95	95	94	92

(20) CHANGES IN CENTRAL VENOUS PRESSURE (CVPP) AT VARIOUS TIME POINTS (MINS)

SL NO.	CVP0	CVP5	CVP10	CVP15	CVP20	CVP25	CVP30	CVP35
1	8	8	7	7	7	6	8	8
2	10	8	8	9	8	10	9	9
3	9	7	7	7	8	8	8	9
4	7	6	6	6	7	8	8	8
5	9	9	9	9	9	10	10	10
6	8	8	8	7	7	6	6	6
7	9	8	9	9	9	8	9	9
8	6	6	8	8	8	8	8	9
9	6	6	7	8	9	9	10	10
10	9	9	6	6	7	7	7	9
11	8	8	6	6	6	7	8	8
12	6	6	6	5	7	7	7	8
13	7	7	8	8	10	10	10	12
14	4	4	7	7	6	6	5	6
15	7	6	7	7	7	8	7	8
16	5	4	5	7	6	6	6	5
17	6	7	7	7	8	6	6	7

18	8	8	8	9	7	8	8	8
19	10	12	11	10	9	9	8	8
20	4	4	6	6	5	6	6	6
21	6	6	7	5	7	7	7	8
22	6	6	8	8	8	8	8	8
23	7	7	7	9	9	9	7	9
24	8	8	8	8	6	8	8	8
25	6	7	7	7	9	9	9	8

(21) CHANGES IN OXYGEN SATURATION (SpO2) AT VARIOUS TIME POINTS (MINS)

SL NO.	SpO2_0	SpO2_5	SpO2_10	SpO_15	SpO2_20	SpO_25	SpO2_30	SpO2_35
1	100	99	100	100	98	100	100	100
2	100	100	100	100	100	99	100	99
3	100	100	98	100	99	100	100	100
4	100	97	100	100	99	100	100	100
5	100	100	100	100	100	100	100	100
6	100	98	100	100	100	100	100	99
7	100	100	100	100	100	100	100	100
8	100	100	100	99	100	98	100	99
9	100	100	100	99	100	100	100	100
10	100	100	100	100	99	100	99	100
11	100	99	100	100	100	98	100	100
12	99	100	100	100	99	100	100	100
13	100	100	100	98	100	100	97	100
14	100	100	100	100	100	98	100	100
15	100	100	100	100	99	100	100	100
16	100	100	99	100	100	100	100	100
17	100	98	100	100	100	100	100	100
18	100	100	99	100	100	100	98	100
19	100	100	99	100	100	98	100	100
20	100	99	99	100	100	98	100	100
21	100	100	100	100	100	100	100	100
22	100	100	100	98	100	100	100	100
23	100	100	100	100	100	99	100	100
24	100	100	98	100	100	100	100	100
25	100	100	100	100	100	100	100	100

(22) CHANGES IN BISPECTRAL INDEX (BIS) AT VARIOUS TIME POINTS (MINS)

SL NO.	BIS_0	BIS_5	BIS_10	BIS_15	BIS_20	BIS_25	BIS_30	BIS_35
1	44	46	54	56	43	40	46	50
2	52	59	54	42	46	58	60	66
3	56	52	50	47	48	50	52	50
4	54	52	54	51	50	48	46	44
5	44	43	43	42	46	48	50	46
6	46	45	43	46	45	48	46	45
7	49	50	52	45	44	48	51	54

8	42	46	46	48	50	52	48	44
9	47	44	45	44	45	46	44	46
10	46	50	48	48	44	45	47	43
11	42	43	46	42	44	44	45	45
12	49	54	56	58	54	54	52	56
13	47	40	44	45	44	42	45	46
14	36	44	43	44	46	43	54	56
15	46	48	50	54	56	56	53	55
16	56	42	44	46	45	47	44	42
17	47	48	54	52	58	60	54	53
18	49	57	54	50	52	52	56	50
19	38	46	44	43	44	45	47	48
20	46	46	48	46	45	44	45	45
21	56	54	56	53	51	57	53	55
22	58	60	52	54	52	55	56	51
23	47	43	44	42	43	44	46	44
24	56	60	64	62	54	55	52	49
25	64	56	55	57	56	53	55	51

(23) TEE TRANSMITRAL BLOOD FLOW PARAMETERS (CONTROL)

SL NO.	E_Vmax_1	A_Vmax_1	E/A_1	DT_1	A_duration_1
1	43.3	55.1	0.78	224	137
2	43.3	61	0.7	212	162
3	42.3	48.6	0.87	228	180
4	54.9	75.1	0.73	237	140
5	48.9	46.2	1	226	121
6	73.3	89.1	0.8	184	145
7	45.8	59.5	0.76	236	148
8	47.7	35.3	1.35	236	137
9	43.9	47.6	0.9	261	130
10	50.2	54.8	0.92	218	155
11	37	26.5	1.39	209	127
12	48.5	57.2	0.84	190	130
13	56.6	49.7	1.13	218	172
14	25.4	58.9	0.43	287	153
15	66.8	86.7	0.77	208	147
16	39.1	42.7	0.9	222	127
17	50.1	60.7	0.82	282	120
18	47	60.2	0.78	231	144
19	51.9	52.6	0.98	262	126.8
20	32	39.6	0.8	251	133
21	45.4	58.9	0.7	265	124
22	60.2	58.2	1	215	164
23	48.8	52.8	0.9	210	132
24	48.5	46	1	240	154
25	42.9	48.4	0.9	231	143

(24) TEE PULMONARY VENOUS BLOOD FLOW PARAMETERS (CONTROL)

SL NO.	S_vmax_1	D_vmax_1	S/D_1	Ar_Vmax_1	Ar_Vmax_dur_1	A-AR 1
1	50.5	32.4	1.56	21.4	82	55.00
2	38	22	1.72	19.5	66	96.00
3	37.7	19	1.98	10.4	81	99.00
4	37.3	18.7	1.99	14.4	87	53.00
5	57.4	39.7	1.44	18.9	95	26.00
6	71.8	19.4	3.7	16.9	88	57.00
7	39.5	24.7	1.6	18.1	123	25.00
8	19.3	16.9	1.1	10.2	92	45.00
9	34.8	35.7	0.97	11.6	95	35.00
10	33.1	21.1	1.56	18.1	116	39.00
11	30.7	26.8	1.11	14.7	61	66.00
12	30.7	15.7	2	12	82	48.00
13	46.4	33.7	1.37	16.5	165	7.00
14	35.3	15.9	2.2	19.8	109	44.00
15	59.7	39.5	1.51	24.1	72	75.00
16	26.5	20.2	1.3	22.2	95	32.00
17	43.8	26.5	1.65	18.3	123	-3.00
18	35.8	24.6	1.5	14	60	84.00
19	31.3	27.5	1.13	14.1	92	34.80
20	33.9	20	1.69	11.6	106	27.00
21	36	18	2	12	110	14.00
22	42	31	1.35	14	152	12.00
23	31	23	1.34	16	102	30
24	38	20	1.9	18	96	58
25	57	40	1.46	17	105	38

(25) TEE TISSUE DOPPLER IMAGING PARAMETERS (CONTROL)

SL NO.	E1_1	A1_1	E1/A1_1	IVRT_1	E_1/E1_1
1	10.3	14.5	0.71	98	4.20
2	8.3	7.16	1.15	95	5.22
3	8.47	7.3	1.16	110	4.99
4	8.09	10.18	0.8	99	6.79
5	13.5	9.85	1.37	120	3.62
6	7.68	8	0.94	99	9.54
7	8.61	8.82	0.97	150	5.32
8	6.85	5.5	1.2	162	6.96
9	6.53	4.87	1.34	144	6.72
10	7.68	5.5	1.4	127	6.54
11	9.98	5.23	1.9	127	3.71
12	8.3	11.7	0.7	132	5.84
13	9.96	5.12	1.94	116	5.68
14	4.56	8.19	0.55	204	5.57
15	7.16	12.3	0.58	85	9.33
16	5.39	8.9	0.6	109	7.25
17	5.08	9.33	0.54	116	9.86
18	4.75	8.09	0.6	155	9.89

19	4.75	7.08	0.67	127	10.93
20	3.01	7.26	0.41	204	10.63
21	3.5	7.5	0.46	157	12.97
22	9.3	8.2	1.12	123	6.47
23	9.4	8.5	1.1	126	5.19
24	9.7	8.6	1.12	125	5.00
25	8.9	7.9	1.1	128	4.82

(26) TEE TRANSMITRAL BLOOD FLOW PARAMETERS (STUDY)

SL NO.	E_Vmax_2	A_Vmax_2	E_2/A_2	DT_2	A_duration_2
1	44.9	48.4	0.9	201	118
2	38.3	39.1	0.97	187	144
3	47.9	35.3	1.35	173	176
4	44.8	63.1	0.7	165	132
5	38.5	30.4	1.26	204	136
6	38	57.8	0.65	176	123
7	47.4	65.2	0.71	195	138
8	46.8	32.9	1.42	215	169
9	47.3	43.4	1.08	180	113
10	47.5	66.9	0.7	173	126
11	49.1	31.6	1.55	190	166
12	37.6	31	1.21	218	151
13	40.1	38.5	1.03	257	148
14	25.4	51.2	0.49	239	120
15	56.2	62.9	0.89	190	173
16	38.5	47.7	0.8	183	123
17	47.2	53.5	0.88	194	140
18	26.2	35.3	0.74	186	130
19	40.6	39.9	1	171	141
20	23.1	28.1	0.8	194	158
21	35.6	46.7	0.76	210	114
22	57	45	1.26	188	154
23	45	50	0.9	184	111
24	45	42	1	187	152
25	40	41	0.97	174	154

(27) TEE PULMONARY VENOUS BLOOD FLOW PARAMETERS (STUDY)

SL NO.	S_vmax_2	D_vmax_2	S/D_2	Ar_vmax_2	Ar_vmax_dur_2	A-AR 2
1	32.4	20.9	1.55	20.6	103	15
2	40.8	25.4	1.6	16.8	116	28
3	30.7	17.2	1.78	11.7	99	77
4	39.1	22.9	1.7	12.6	92	40
5	36.2	22.3	1.62	11.6	97	39
6	60.2	20.7	2.9	12.7	70	53
7	32.7	18.8	1.73	11.1	60	78
8	16.9	17.6	0.96	11.1	123	46
9	45.6	28.8	1.58	13.5	77	36

10	59.2	19.7	3	9.15	72	54
11	18.1	21.9	0.8	9.87	85	81
12	43.6	25.9	1.65	13.5	119	32
13	45.4	37.5	1.21	21.7	137	11
14	34.8	12.5	2.8	14.2	92	28
15	37.5	29.4	1.27	18.2	60	113
16	43.3	26	1.7	23.1	109	14
17	40.5	26.5	1.52	20.7	116	24
18	26.8	21	1.27	8.26	85	45
19	24.1	21.7	1.11	12	120	21
20	33	13.1	2.51	7.22	109	49
21	32	20	1.6	10.1	98	16
22	40	26	1.5	12	132	22
23	34	21	1.6	16.8	85	26
24	36	17	2.1	15.6	89	63
25	54	34	1.6	14.2	92	62

(28) TEE TISSUE DOPPLER IMAGING PARAMETERS (STUDY)

SL NO.	E1_2	A1_2	E1/A1_2	IVRT_2	E_2/E1_2
1	5.32	8.2	0.65	148	8.44
2	7.16	6.43	1.1	102	5.35
3	6.73	4.86	1.4	97	7.12
4	4.25	6.74	0.62	134	10.54
5	9.65	6.43	1.5	113	3.99
6	6.5	4.87	1.34	120	5.85
7	5.6	7.68	0.72	165	8.46
8	7.8	4.25	1.8	109	6.00
9	8.3	7.8	1.06	141	5.70
10	8.09	7.47	1.08	123	5.87
11	11.8	5.8	2	143	4.16
12	6.64	5.5	1.2	106	5.66
13	5.46	4.15	1.31	99	7.34
14	4.85	7.47	0.64	180	5.24
15	4.87	7.33	0.67	127	11.54
16	6.64	8.71	0.8	137	5.80
17	5.86	6.39	0.91	74	8.05
18	3.66	6.61	0.55	148	7.16
19	4.28	5.76	0.74	116	9.49
20	4.2	2.9	1.4	165	5.50
21	3.8	6.2	0.6	160	9.37
22	8.8	7.2	1.2	110	6.48
23	8.5	7.3	1.16	100	5.29
24	8.4	7.8	1	98	5.36
25	7.5	6.2	1.2	87	5.33