Comparative evaluation of the effects of Etomidate versus conventional induction techniques on hemodynamic stability during induction in patients with impaired left ventricular function undergoing cardiac surgery.

A Thesis submitted to the Tamil Nadu Dr. M.G.R Medical University in partial fulfillment of the degree M.D ANAESTHESIA.

By

Dr. J. Felinda Angelin

Christian Medical College and Hospital, Vellore,

Tamil Nadu, 632004 – India.
CERTIFICATE

This is to certify that the dissertation entitled “Comparative evaluation of the effects of Etomidate versus conventional induction techniques on hemodynamic stability during induction in patients with impaired left ventricular function undergoing cardiac surgery” is a bonafide work of Dr. J.FELINDA ANGELIN in partial fulfillment of the requirements for the M.D. Anaesthesiology (Branch X) degree examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai, to be held in April 2017.

Dr. ANNA PULIMOOD
Principal,
Christian Medical College,
Vellore

SIGNATURE OF THE GUIDE                      SIGNATURE OF THE H.O.D

Dr. RAJ SAHAJANANDAN                      Dr. SAJAN PHILIP GEORGE
Professor
Department of Anaesthesiology
Christian Medical College
Vellore-632004

Professor and Head
Department of Anaesthesiology
Christian Medical College
Vellore- 632004
DECLARATION

I hereby declare that this dissertation titled “Comparative evaluation of the effects of Etomidate versus conventional induction techniques on hemodynamic stability during induction in patients with impaired left ventricular function undergoing cardiac surgery” was prepared by me in partial fulfilment of the regulations for the award of the degree of M.D ANAESTHESIA of the Tamil Nadu Dr. M.G.R Medical University, Chennai. This has not formed the basis for the award of any degree to me before and I have not submitted this to any other university previously.

J. Felinda Angelin

Vellore
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Introduction

Coronary artery disease is prevalent worldwide, and many in India are also affected due to the increasing sedentary lifestyle and high prevalence of diabetes and hypertension...

In patients with coronary artery disease, induction of anesthesia is challenging because the circulatory system cannot tolerate depression. The main aim should be to avoid hypotension, minimize the stress response to laryngoscopy and to maintain the balance between myocardial oxygen supply and demand. This challenge is exaggerated when you are dealing with a patient whose left ventricular function is impaired. Avoidance of hypotension is crucial as it is associated with increased morbidity and mortality. Induction of anesthesia is associated with loss of sympathetic tone, and myocardial depression. Hypotension has been defined as a decrease in mean arterial pressure (MAP) less than 60 mm Hg or a decrease of > 40% from the baseline. An episode of hypotension lasting for more than 1.5 minutes is shown to be associated with...
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INTRODUCTION

Coronary artery disease is prevalent worldwide, and many in India are also affected due to the increasing sedentary lifestyle and high prevalence of diabetes and hypertension...

In patients with coronary artery disease, induction of anesthesia is challenging because the circulatory system cannot tolerate depression. The main aim should be to avoid hypotension, minimize the stress response to laryngoscopy and to maintain the balance between myocardial oxygen supply and demand. This challenge is exaggerated when you are dealing with a patient whose left ventricular function is impaired. Avoidance of hypotension is crucial as it is associated with increased morbidity and mortality. Induction of anesthesia is associated with loss of sympathetic tone, and myocardial depression. Hypotension has been defined as a decrease in mean arterial pressure (MAP) less than 60 mm Hg or a decrease of > 40% from the base line. An episode of hypotension lasting for more than 1.5 minutes is shown to be associated with a 13.3 % increase in hospital stay and 8.6% increase in death. Intraoperative hypotension has been shown to be associated with myocardial ischemia as evidenced by elevated troponin T levels(1). Intraoperative hypotension is associated with the occurrence of myocardial ischemia as evidenced by elevated Troponin levels. Given the high risk of poor outcomes due to post induction hypotension, an ideal induction agent should be the one
which produces minimal changes from baseline hemodynamic variables and suppresses the stress response to intubation.

Normally laryngoscopy and intubation produce hypertension and tachycardia or rarely bradycardia as result of autonomic stimulation which can jeopardize the balance between myocardial supply and demand. Suppression/ minimizing this response is an important aspect of anesthesia induction.

**However our search for an ideal agent is still far from reality.**

Various intravenous drugs are used for induction of anesthesia in these patients, the common ones are thiopentone, propofol, ketamine, etomidate and midazolam. We have to select an anesthetic that has the balance between prevention of hypotension and avoiding a surgical stress response. Etomidate has a stable cardiovascular profile and is considered by many as an ideal induction agent in patients with significant coronary artery disease and left ventricular dysfunction. Use of Etomidate is associated with adrenal suppression even after single dose. Cortisol which is a stress hormone, is also involved in maintaining the vascular tone, gets suppressed by etomidate. So, there can be increasing requirement of vasopressors postoperatively and may lead to poorer outcome in patients with sepsis. However the evidence is conflicting.
Midazolam is another induction agent with good cardiovascular stability and is effective in suppressing the stress response to laryngoscopy and intubation. However, combining midazolam with fentanyl may result in hemodynamic instability.

We propose a study to compare etomidate and midazolam for induction of anesthesia in patients with impaired left ventricular function undergoing coronary artery bypass graft. We will compare the effects of these drugs on hemodynamic stability and the ability to prevent intubation response. We will also study whether the use of etomidate results in significant adrenal suppression and general outcomes.
AIMS AND OBJECTIVES

➢ Primary aim:

1. To compare the effects of Etomidate and Midazolam on hemodynamic stability during induction of anesthesia in patients with impaired left ventricular undergoing Coronary artery bypass grafting.

2. To compare their efficacy in minimizing hemodynamic response to intubation.

➢ Secondary aim:

To measure serum cortisol levels in both group of patients to see if there is any adrenal suppression with a single dose of etomidate used during induction.
REVIEW OF LITERATURE

Global burden

Coronary artery disease is a leading cause of death and disability in developed countries. Over the age of 35, one third or more of the mortality is due to ischemic heart disease. The prevalence of coronary artery disease worldwide is 70%. There are so many risk factors which promote coronary artery disease like smoking, dyslipidemia, diabetes, and hypertension.

In 2010 the American Heart Association, Heart Disease and Stroke Statistics(NHANES) in an update has reported that IHD prevalence to be 17.6 million. Among them myocardial infarction(MI) prevalence was 8.5 million and the prevalence of angina pectoris was 10.2 million (2). In both sexes there was a progressive increase in the prevalence. Since 1990 there was a 41% increase of deaths due to cardiovascular disease, that is 17.3 million deaths worldwide.(3) The age-standardized death rate has decreased by 22 percent in the same period.

During 1988-1994 and 1999-2004 time periods, in age group of 35-54 years, prevalence of MI was compared against sex in a NHANES data 2009 report. It was found that men had a greater prevalence than women in both the time period (2.5 in men versus 0.7 in women, and 2.2 in men versus 1.0 in
women) and there was a declining trend in men and increasing trend in women.

INCIDENCE

In the original Framingham study, for an individual aged more than 40 years in a cohort of 44 years of follow up, the lifetime risk to develop CHD is 49 percent in men and 32 percent in women (4–6). The risk was found to be 35 percent in men and 24 percent in women, in individuals nearing 70 years. The incidence of coronary events increases with age, in women MI presents later by about 10 years. Women lag behind men in incidence by 20 years in the incidence of MI and sudden death.

The incidence at ages 65-94 years compared to ages 35-64 years, more than doubles in men and triples in women (7–9). The annual incidence rate was found to be 12 per 1000 in men below 65 years of age, this was more than the rate of all the other atherosclerotic cardiovascular events combined (7 per 1000); in women, it equals the rate of the other events (5 per 1000). After 65 years of age, the leading health problem among the elderly is coronary artery disease. Of the atherosclerotic cardiovascular events in men, coronary events form 33 to 65 percent and 28 to 58 percent in women. Below 75 years of age in women, coronary disease presents more often as angina pectoris than MI. (5,6). Having said that, 80% angina in women is more often uncomplicated whereas 66% of angina in men often occurs after a MI. At all ages in men, myocardial infarction occurs, among them 20% have pre-existing long-
standing angina. If the MI is silent or unrecognized, the percentage is even lower (5,6).

An analysis from the (NHANES) I Epidemiologic Follow-up study compared two cohorts of subjects, from 1971 to 1982 (10,869 patients) and from 1982 to 1992 (9774 patients)(10). In the yearly follow up per 10,000 persons, the incidence of CHD decreased from 133 to 114 cases. There was an overall large decline in cardiovascular disease (from 294 to 225 cases per 10,000 persons per year). In Olmsted County, Minnesota, a report from the Mayo Clinic examined the incidence of CHD over time (11). During the interval from 1988 to 1998, there was a decrease from 57 to 50 cases per 10,000 persons in the age-adjusted incidence of any new coronary disease-like MI, sudden death, unstable angina, or angiographically diagnosed CHD (relative risk 0.91, 95% CI 0.82-1.01).

In 2014 in a study done by World Health Organization, it was found that over 4 million annual deaths are due to cardiovascular disease, from data collected from 49 countries in Europe and northern Asia(10).

- In India, the prevalence of ischemic heart disease could not be fully explained by traditional risk factors (12).
- In China, due to higher cholesterol levels, there have been an increase in CHD mortality in Beijing.
- Due to a higher prevalence of physical inactivity, obesity and smoking in Latin America, the vascular disease rates are comparatively higher than the United States.(13).
There has been a relative increase in non-ST elevation MI (NSTEMI) in relation to ST elevation MI with time (14–16). For example, a report from the National Registry of Myocardial Infarction 1 to 5 reviewed over 2.5 million MIs between 1990 and 2006 (14) and found that the proportion of MIs due to NSTEMI increased from 19 percent in 1994 to 59 percent in 2006. This change in proportion was associated with an absolute decrease in the incidence of STEMI and either a rise (using MI defined either CK-MB or troponin criteria) or no change (using MI defined using only CM-MB criteria) in the rate of NSTEMI (13).

**INDIAN BURDEN OF DISEASE**

India is going through a phase where the communicable disease is decreasing, and the non-communicable diseases are on the rise. This has led to a dual burden. There has been a disturbing increase over the few years in the prevalence of cardiovascular disease in India and South-east Asia. In India, the prevalence over the past 40 years has increased 4-fold. In a study done from across the country, the prevalence was found to be 7-13% in urban (17,18) and 2-7% in rural (19,20) regions. In Chennai the deaths due to cardiovascular causes was highest at 38.6%. Cardiovascular deaths were highest in Chennai 38.6% as reported by Gajalakshmi et al (21).

The Global Burden of Diseases Study has reported that during 1990 the disability-adjusted life years lost due to CHD in India was 5.6 million in men and 4.5 million in women; it is expected to rise to 14.4 million in men and 7.7
Risk factors of CAD like dyslipidemia, central obesity, hypertension, diabetes, physical inactivity and smoking have alarmingly increased which explains the overpowering disease burden. Over the past two decades, there has been rapid urbanization and lifestyle change. Previous studies which were done in migrant Indians were misinterpreted that they are genetically predetermined to develop the disease and that conventional risk factors do not contribute to the CHD prevalence among Indians. The high prevalence and occurrence of CHD prematurely cannot be attributed to the conventional risk factors.

However, the large INTERHEART study an international study recruiting 30,000 people from 52 countries, found that most of the CHD burden was due to conventional risk factors. It also recruited a large number of Indians. The aim was to establish the risk factors associated with myocardial infarction. The influence of factors like nationality, sex and age on the prevalence was studied. The secondary aim was to find the overall population attributable risk and in various subgroups. The influence of obesity, physical inactivity, alcohol consumption was studied. It was seen that at the age of 40 or younger, the first attack of MI was seen in the Middle East and Africa and South Asia with an incidence of 12.6, 10.9, and 9.7 respectively. Psychosocial factors, abdominal obesity, diabetes, hypertension, dietary patterns and waist-hip ratio were the next most important risk factors in men and women.
There are over 32 million diabetics in India. In 2025 it may reach 57.2 million. In 2000 it was reported that the prevalence of type 2 diabetes in urban Indian adults has increased from less than 3.0% in 1970 to about 12.0% in 2000. In a survey done by ICMR the prevalence of diabetes was 3.8% in rural areas and 11.8% in urban areas. In 2025, the count of hypertensives will rise from 118 million in 2000 to 214 million.

Globalization due to increasing connectivity among countries, increased trade and finances, acceptance to ideas have contributed to the disease burden. In the last decade, the prevalence and production of tobacco products has increased by more than double in the developing world compared to 36% reduction in the developed world.

Among the 1.1 billion smokers worldwide, India accommodates 182 million. In tobacco production and consumption, India is the third largest country in the world, in both tobacco production and consumption. The production of tobacco products have increased markedly in the developing countries. Except the poorest countries, all other countries have replaced the traditional diet rich in fruit and vegetables by a diet rich in calories provided by animal fats and low in complex carbohydrates. Such changes will in general lead to increased rates of many non-communicable diseases, although not necessarily stroke rates.
HISTORY OF CARDIAC SURGERY

In 1801, Francisco Romero, in 1810 Dominique Jean Larrey, in 1891, Henry Dalton and in 1893, Daniel Hale Williams were the first ones to operate on the pericardium. On 4 September 1895, in Rikshospitalet Kristiania, the first surgery on the heart was performed by a Norwegian surgeon Axel Cappelen. On September 7, 1896, Dr. Ludwig Rehn of Frankfurt, Germany, by repairing a stab wound to the right ventricle did the first successful surgery on the heart. After World War II, cardiac surgery changed significantly. In 1948, four surgeons independently did work on mitral valve repair. In 1947, Thomas Holmes Sellors operated on a Fallot's tetralogy in Middlesex hospital. Dr. Wilfred G. Bigelow found out that a motionless and bloodless field made the repair of intracardiac pathologies easier. Correction of congenital heart disease was done by Dr. C. Walton Lillehei and Dr. F. John Lewis at the University of Minnesota on September 2, 1952. In 1956 Dr. John Carter Callaghan performed a number of firsts in heart surgery, including the first documented open-heart surgery in Canada. The first successful use of extracorporeal circulation by means of an oxygenator was reported by Dr. John Heysham Gibbon at Jefferson Medical School in Philadelphia in 1953.

Coronary Artery disease

Coronary artery disease is most commonly defined as more than 50% luminal stenosis of any epicardial coronary artery. It is most commonly due to atheromatous plaque. Coronary artery disease manifests as stable angina, acute
coronary syndrome, congestive heart failure, silent ischemia and sudden cardiac death.

Acute coronary syndrome ranges from unstable angina to STEMI. It results from acute thrombosis of coronary artery at the site of atheromatous plaque rupture or ulceration.

SYNTAX is the most important trial of CABG and PCI. Report of the final 5 year follow up by Friedrich Mohr et al is as follows:

There was a significant difference in Major adverse cardiac and cerebrovascular events (MACCE). It was 26·9% in the CABG group versus 37·3% in the PCI group (p<0·0001).

The incidence of cardiac death was 5·3% vs 9·0% with p=0·003, myocardial infarction was 3·8% vs 9·7% with p<0·0001, and repeat revascularisation 13·7% vs. 25·9% with p<0·0001. There was no significant difference in all-cause death (11·4% vs 13·9%; p=0·10) or stroke (3·7% vs 2·4%; p=0·09)(29)

CABG SURGERY

In 1910 A. Carrel attempted the first CABG in animals. In 1954, G. Murray used the internal mammary artery (IMA) as a graft in CABG. R. Goetz performed the first reported CABG using the IMA in humans. He used
the suture less technique in 1960. The technique of sutured bypass grafting was introduced in 1964 by V. Kolessov. From 1962 to 1967, saphenous vein was used as autogenous grafts in CABG. By 1990s Off-pump coronary artery bypass came into existence. This was done without cardiopulmonary bypass.

The goal is to revascularize the area of myocardium that was perfused previously by coronary arteries with a stenosis of more than 50%. A durable conduit is needed for this purpose.

A systemic inflammatory response is triggered in patients undergoing cardiothoracic surgery with cardiopulmonary bypass (CPB) as a result of the combination of surgical trauma, activation of blood components in the extracorporeal circuit, ischemia/reperfusion injury, and endotoxin release (30–33). There is evidence for activation of all the body’s major host defensive pathways, including complement, coagulation, kinins, fibrinolysis, leukocytes, platelets, and inflammatory cytokines (33–42). This broad wave of systemic activation has been linked to adverse clinical outcomes ranging from mild adverse effects (fever or diffuse tissue edema), to moderate adverse effects (pathological hemodynamic instability or coagulopathy), to severe complications (acute organ injury requiring mechanical support), and even mortality (43–45). The sympathetic nervous system stimulates the cardiovascular system. This causes catecholamine levels to increase leading to tachycardia and hypertension, which can cause myocardial ischemia and infarction (46–48). Short lived effects can have dire consequences on the
coronary circulation of high-risk patients causing morbidity and mortality.(49,50).

A best available summary of the evidence suggests that the use of OPCAB may reduce myocardial injury (troponin and CKMB), but this could not be linked in an obligate relationship with inflammatory suppression.(51) There were eight RCTs on approaches to minimize the surface area of the extracorporeal circuit, and three of these eight achieved clinical benefit. There were 14 RCTs examining different biocompatible surface coatings of which six indicated a clinical benefit. Heparin was the most widely studied biocompatible coating plus one paper was a direct comparison of two different types of heparin-coated circuits. Poly-2-methoxyethylacrylate and amphophilic silicone–caprolactone oligomer were also studied as surface coatings. There were eight RCTs studying leukocyte depletion, seven of which used the same arterial line leuko-depleting filter. Two of these eight studies were assigned a clinical benefit. There were 13 RCTs and one Cochrane database review (52) on steroid interventions. Among the 13 RCTs, three were assigned a clinical benefit. Five RCTs investigated the use of complement inhibitors, three of which found a clinical benefit. There was one RCT and one meta-analysis for aspirin given preoperatively, and neither study was able to demonstrate a clinical benefit.
There were three RCTs examining different methods to deliver nitric oxide (NO) to patients perioperatively: all demonstrated clinical benefit. There were three RCTs examining administration of neutrophil elastase inhibitors were adjudged clinically beneficial. There were two RCTs studying propofol anesthesia. Both studies demonstrated a clinical outcome improvement. There were two RCTs from the same research group on the bronchodilator aminophylline. Both of these small studies (n = 30) demonstrated a clinical benefit. There were two RCTs on sevoflurane anesthesia, only one of which demonstrated an improvement in a clinical outcome. There was one RCT on intensive insulin therapy using the Portland Protocol(53) in patients with no history of diabetes. This well-designed study (n = 100) showed a clinical benefit with significantly shortened intensive care unit stay and myocardial protection. There was one RCT on fluvastatin administered for 3 weeks up to the day of surgery; this study demonstrated clinical benefit. There was one RCT on propionyl L-carnitine administration in a diabetic cohort, which assigned a clinical benefit for this intervention. There were three RCTs on ultrafiltration using three different ultrafiltration techniques. However, none of the trials recorded a significant depletion of inflammatory biomarkers and none achieved a clinical benefit. There were no indications of negative patient outcomes.
Induction of anesthesia

Propofol, Etomidate, barbiturate, acts on \( \gamma \)-aminobutyric acid type A receptors. A state of sedation is induced with a small dose of propofol, barbiturate, and etomidate (54). When the drug is given, it causes excitation (55). At that time there are random movements, mumbled speech, and euphoria. It is accompanied by an increase in beta activity on EEG (13 to 25 Hz) (55–58). This state is called paradoxical because the drug causes excitation instead of unconsciousness.

As the induction agent is given over 10-15 seconds, respiration becomes jerky, bag and mask ventilation is started to support breathing. Simultaneously, the patient becomes unresponsive, and muscle tone is lost. Further on, when the anesthesiologist asks the patient to follow the finger, eye movements stop, and nystagmus may occur and there is increased blinking. Oculocephalic and eyelash reflex, corneal reflex is also lost (83) However, pupillary reflex remains intact (84). There can be fluctuations in blood pressure, while tachycardia occurs. Opioid or benzodiazepines are given to suppress the tachycardia, vasopressors are given to maintain blood pressure.

Problems during induction

There is no standard definition of intraoperative hypotension, as a result it is difficult to assess the incidence across various studies. Hypotension mostly occurs between start of induction and starting of surgery. Various parameters
have been analyzed such as baseline variation, a decrease in systolic arterial pressure or mean arterial pressure (MAP) under a set-point, combination of parameters, period of hypotension, and vasopressor requirement or fluid requirement. (61) It was found that hypotension occurs in 5-99% of patients during anesthesia (Bijker et al) (61). There have been no clear definitions of the threshold and duration of hypotensive episodes which can lead to complications. 20% or more Systolic arterial pressure decrease is defined as perioperative hypotension. In their study, Reich et al showed that hypotension occurred more often 5–10 minutes after induction rather than the initial 0–5 minute period (62). A decrease in MAP more than 40% or <70 mmHg, or <60 mmHg is defined as hypotension. The incidence of hypotension was 7.7% in ASA I–II, 12.6% in ASA III–V patients respectively. Various predictors of hypotension included: ASA III–V, MAP <70 mmHg, age ≥50 years, high dose fentanyl and propofol use at induction. Many studies have indicated that cardiac complications result from hemodynamic instability during surgery. Acute intraoperative hypertension alone is not known to cause complications. A MAP decrease of 40% or <50 mmHg MAP intraoperatively are associated with coronary events in high-risk patients. (63). After a noncardiac surgery, episodes of MAP <55 mmHg which are short lived can cause acute kidney injury and myocardial ischemia. (64) The blood pressure threshold and duration which can be associated with perioperative stroke is not established yet. (65) Hypotension at the time of surgery is the most frequent causative factor related to mortality in anesthesia. (66)
**Stress response to intubation**

Laryngoscopy and endotracheal intubation forma major part of general anesthesia for cardiac surgery (67). Laryngoscopy and orotracheal intubation are potent stimuli, which can provoke hemodynamic response like hypertension and tachycardia which can lead to myocardial ischemia, ventricular arrhythmia, left ventricular failure and cerebral hemorrhage. The mechanism of these responses is explained by somatovisceral reflexes. During laryngoscopy, stimulation of proprioceptors at the base of the tongue, induces impulse dependent increase in blood pressure, heart rate, and catecholamine surges. Repeated orotracheal intubation elicits augmented hemodynamic and epinephrine responses and some vagal inhibition of the heart. These incidences are harmful in such a group of patients like coronary artery disease, cardiac arrhythmias, cardiomyopathy, congestive heart failure, hypertension and geriatric population. To suppress the stress response to laryngoscopy and intubation various drugs like barbiturates, calcium channel blockers, vasodilators, beta blockers, and opioids have been tried at regular intervals. Hence there is a need to attenuate hemodynamic responses to laryngoscopy and surgery without undue hypotension.

In 1940, Reid and Brace, first described a hemodynamic response to laryngoscopy and intubation (68). It leads to an average increase in blood pressure by 40-50% and 20% increase in heart rate (69). The increase in blood pressure and heart rate is usually transient and variable, but can be
unpredictable and life-threatening if left unaddressed. For most patients, the hemodynamic response to the stress of laryngoscopy and endotracheal intubation does not present a problem(70). However, cardiac patients respond to anesthetic induction and endotracheal intubation with an increase of blood pressure and heart rate and are more prone to develop hemodynamic instability (71). The delicate balance between myocardial oxygen demand and supply is altered due to hemodynamic changes caused due to intubation. This may precipitate myocardial ischemia in patients with coronary artery disease (129). Laryngoscopy itself is one of the most invasive stimuli during endotracheal intubation (70,72). Many anesthesiologists agree that a skilled anesthesiologist applies only a small force to the patient’s larynx when using a laryngoscope and that reducing the force on the larynx might prevent excessive hyperdynamic responses to endotracheal intubation (73–75). After seconds of direct laryngoscopy, hemodynamic changes occur, leading to further increase in heart rate and blood pressure with passage of the tracheal tube. The first is the response to laryngoscopy and the second is the response to endotracheal intubation. The component which is responsible for the hyperdynamic response is not known. Singh et al., while doing a study on different induction agents in Coronary artery disease, showed that stress response on intubation was most obvious when etomidate was the induction agent in patients with coronary artery disease while midazolam was most effective in preventing intubation stress(76). Hemodynamic changes were lesser when intubation was done with the Airtraq, when compared to the Macintosh laryngoscope (77,78). Thus,
many studies have focussed on stress response to endotracheal intubation, high doses of opioids, \( \alpha_2 \)-adrenergic receptor agonists, \( \beta \)-adrenergic blocking drugs or other antihypertensive drugs and a number of drugs have been used to suppress the hemodynamic response(48,49,79–89)

A wide variety of pharmacological agents were used to attenuate the hemodynamic responses to laryngoscopy and endotracheal intubation like lignocaine,(90), fentanyl(91), alfentanil,(92), remifentanil,(143)nifedipine,(93) beta-blockers,(94) gabapentin,(95)magnesium sulfate,(96) verapamil, nicardipine, diltiazem(97)with varying results. Previous studies(97–101)have also documented that nitroglycerin does not attenuate the rise in heart rate after intubation, which can be attributed to reflex tachycardia produced by vasodilation. The principal advantage of using nitroglycerin is that, while a desirable and transient hypotension is achieved, cardiac output is not likely to decrease. Preload reduction and accompanying decrease in ventricular end-diastolic pressure(98), reduces myocardial oxygen demand and increases endocardial perfusion by dilating the coronary vessels. NTG may increase the coronary blood flow and oxygen delivery to the myocardium. Because of its predominantly venodilatory action, it seems to be the best choice in patients with low cardiac output and moderately elevated resistance.(102)

Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased
by both the arterial and venous effects of nitroglycerin resulting in a more
favorable supply-demand ratio (98). Esmolol given IV in a dose of 1 mg kg\(^{-1}\)
before intubation suppressed the stressor response due to intubation (Bostana
and Eroglu (2012)) (103). Lidocaine has been a popular agent for attenuating
circulatory responses. Lidocaine causes depression of cardiovascular system
and vasodilation of the peripheral vasculature (104). The airway reflexes due to
tracheal irritation are attenuated. Its analgesic and antiarrhythmic action have
been fully made use of in cardiac anesthesia. The effects have been shown to be
beneficial in some (105) while other studies indicated that there is no effect
when it is given 1-3 minutes before the time of laryngoscopy (106, 107). Lidocaine in a dose of 1.5 mg/kg and esmolol in a dose of 2 mg/kg
were effective in attenuating the response to laryngoscopy and intubation.
There were no harmful effects reported. Tachycardia and hypertension are
known to contribute to myocardial infarction perioperatively and is an
important factor leading to morbidity and mortality (108). Hence it can be
concluded that the quest for ideal induction agent is still elusive.

**Hemodynamic goals in CABG**

After induction and intubation, there is hypotension and there is intense
surgical stimulus like skin incision and sternotomy that produces hypertension,
tachycardia. The main aim during anesthesia is suppression of sympathetic
responses to laryngoscopy, intubation. Steps of surgery like skin incision,
splitting of sternum, and spreading which can cause massive response should
be avoided. Anesthetic drugs cause vasodilation and depression of cardiovascular system, leading to hypotension which has to be prevented. One induction agent is not favorable for every CABG patient, and anesthesia has to be tailored for each individual to achieve stability in hemodynamics. (109,110)

Since many years, there have been several anesthetic techniques used with their own adverse cardiac effects, inhalational agents at increased doses causing depression of cardiac system, absence of myocardial depression with increased doses of opioids, isoflurane causing coronary vasodilatation leading to steal phenomenon. Another concern is interactions due to pre-op medications, beta blockers causing cardiovascular depression, hypotension due to ACE inhibitors or ARB (111–113). The underlying principle is that oxygen supply and demand ratio should not be altered to avoid injury to myocardium. Now-a days surgical management is moving on to accelerated recovery protocols or fast track management (114,115). Efforts are on to improve the final outcome and to decrease costs which lead to decreased duration of in-hospital stay (114,115).

High-dose opioids with benzodiazepines have been used since the 1970s and 1980s. Eventually volatile anesthetics became more popular, due to their protective effect on the myocardium. However, inhalational agents are not
better when compared to intravenous agents in terms of advantage in the rate of mortality. Hence, opioids have been given a secondary role (116,117).

Patients can be optimized by 1) preoperative assessment done carefully, risk factor modification 2) all medications should be handled properly in the preoperative period 3) monitoring cardiovascular system carefully, inserting a central venous line 4) amnesia, analgesia, and muscle relaxation is induced 5) a smooth progress to the immediate postoperative period. The goal is to extubate early, mobilize the patient, and discharge early.

During CPB, changes in hemodynamics or hormonal changes which can cause ischemia of the myocardium or have a harmful effect on metabolism of the myocardium should be prevented. Appropriate management and careful monitoring is required. Close interaction between the surgeon, anesthesiologist, is needed particularly when the heart, great vessels are being manipulated.

**Anesthetic goals in patients with LV dysfunction**

In patients with LV dysfunction, in order to increase blood pressure and cardiac output, various mechanisms are activated. To increase the circulating blood volume several neurohumoral pathways are activated. The sympathetics cause an increase in heart rate and myocardial contractility, vasoconstriction of the arteriolar system in splanchnic vascular system, and stimulation of the juxtaglomerular apparatus of the kidney to secrete renin. Activation of the Renin–angiotensin system causes vasoconstriction of the arteriolar system,
retention of water and sodium, and release of aldosterone. Aldosterone increase leads to sodium and water retention. Additionally, vasopressin released from the hypothalamus due to baroreceptor and osmotic stimuli, cause water reabsorption from the renal collecting duct. Eventually these mechanisms, even though they are beneficial, aggravate ischemia, dysrhythmia, cause endothelial dysfunction, promote cardiac remodeling and are toxic to myocytes.

Any deterioration in the structure or function in the filling of left ventricle, or systolic ejection results in heart failure. Changes in hemodynamics and drugs used in anesthesia can have a harmful effect on the diastolic function of the left ventricle.

Arrhythmia and myocardial ischemia affect diastolic time. Any preexisting dysfunction in diastole is decompensated. Diastolic time is shortened by tachycardia and left ventricular filling is impaired. Hypo- or hyper-kalaemia, anaemia, or hypovolemia cause rhythm disturbances. Tachycardia can be prevented by beta-blockers or calcium-channel blockers and left ventricular filling is improved (118, 119).

Myocardial relaxation is slowed significantly when there is myocardial ischemia or sudden volume loading or position changes. Myocardial ischemia may cause rhythm changes which can precipitate diastolic dysfunction of the left ventricle. Myocardial ischemia is the imbalance between myocardial blood supply and demand. It can be multifactorial in cardiac surgery. It can happen
due to native coronary artery disease, hypotension at the time of induction, inadequately myocardial protection, inadequate surgical correction (poor target vessels, poor conduits) graft kinking and graft thrombosis.

Thus, when dealing with suspected diastolic heart failure, prevention of ischemic episodes should be the mainstay of management. Beta-blockers are the best drugs known, to decrease oxygen consumption of the myocardium. The mortality due to coronary events overall has been decreased by use of beta-blockers perioperatively.\((120,121)\). It is not known whether this line of management is still suitable for diastolic heart failure. There have been less studies on the effect of intravenous agents on diastolic properties, however, the effect of volatile agents has been extensively studied. Left ventricular diastolic function is not affected by inhalational agents like sevoflurane and desflurane, as well as opioids or muscle relaxants.

**LV DYSFUNCTION AND ANESTHESIA**

Persons with a healthy heart have good cardiac function. However, patients with LV dysfunction have limited cardiac reserve. Since most of the anesthetics that we use routinely are associated with cardiovascular depression the anesthesiologist is placed in a very challenging situation.

Anesthetics depress the sympathetics and these patients rely on the sympathetic system to maintain a good cardiac output. The anesthetics can
cause myocardial depression directly or can indirectly affect the cardiovascular control mechanisms. Initially it was thought that LV diastolic dysfunction was primarily due to systolic dysfunction, but now it is being seen that diastolic dysfunction alone can affect the overall performance of the heart.

In a healthy heart, cardiac output is affected by changes in preload, however in patients with LV dysfunction, it is very sensitive to changes in afterload. Hence arterial vasodilation can improve cardiac output. After anesthetic induction, venodilation occurs leading to decreased cardiac output. In the absence of a coronary intervention, data suggests that before a non-cardiac surgery, ≥60 days should elapse after a MI. MI which has occurred in the last 6 months before a non cardiac surgery is defined as recent MI. It was also an independent risk factor for stroke perioperatively, this was linked with 8-times increase in the mortality rate perioperatively (122). Given the fact that adults more often are affected with diseases like coronary artery disease, stroke, and diabetes mellitus, age plays a major role (123). When they come for noncardiac surgery, risk of MACE increases overall. Another important risk factor for stroke in perioperative period is age more than 62 years (125). There was a higher incidence of acute ischemic stroke, among older adult patients (those >65 years of age) than those ≤65 years of age undergoing noncardiac surgery (124). Complications in the postoperative period was higher in those who had poor cognition, and who had to rely on others for activities of daily
living. Hence, the duration of hospital stay increased (126). A history of stroke is a risk factor to develop MACE perioperatively (122).

**DRUGS USED FOR ANESTHESIA INDUCTION**

**FENTANYL**

It was invented by Paul Janssen (1926–2003) (127–130). It is a derivative of phenylpyperidine. It is 100 times more potent than morphine. It is an agonist at the mu receptor. It has great analgesic properties, and till it causes unconsciousness, produces increase in analgesia depending on the dose given. Along with fentanyl, other agonists are hydromorphone, morphine, and oxymorphone. Compared with nalbuphine, an agonist at the kappa receptor, it has greater effects on analgesia. (Morgan et al., 1999). The ED$_{50}$ was 0.08 and 95% limits were 0.045 to 0.142 mg/kg (131). The LD$_{50}$ in humans is unknown. After injecting, fentanyl quickly enters into the CSF. The $T_{\text{max}}$ was 2.5–10 minutes. (Hug & Murphy, 1979) and the $T_{\text{max}}$ in brain was 10–20 min (Ainslie et al., 1979). The concentrations of fentanyl were found to be equal to that of plasma, later it was lower than the concentration in plasma. (Hug & Murphy, 1979). Concentrations in brain decreased slowly than that of plasma. In a study by Ainslie et al in 1979, it was found that in a duration of 30 min–2 hrs during the study, the concentrations in brain exceeded plasma concentrations. Due to its lipophilic properties, great amounts of the drug are found in the brain. Metabolism and excretion of H-fentanyl occurred in urine and feces, following IV and subcutaneous injection (132) (Ohtsuka et al., 2001). After a
single injection of H-fentanyl, 4% of the drug and 36% of the overall dose was found in 6 hour urine collection (132) (Murphy et al., 1979). Cytochrome P450 is responsible for metabolism. It is dealkylated to nor fentanyl (Feierman, 1996; Feierman & Lasker, 1996; Labroo et al., 1997). Other metabolites were despropionylfentanyl and hydroxyfentanyl.

The duration of analgesia lasts for 30 minutes. There was minimal depression of cerebral cortex. The alterations in respiration are long lasting than the effect of analgesia. At doses in therapeutic range, there was no significant cardiovascular effects. Fentanyl binds to human plasma proteins and rapidly distributes with sequestration in fat. Metabolism occurs in the liver and excretion through the kidney. Elimination half-life ranges from 6 - 32 h. After intravenous injection the effect starts quickly, and it takes 7 to 8 mins after intramuscular dose. After IV injection, it peaks in 5 to 15 min. Duration of the analgesic effect lasts for 1 to 2 hrs on intramuscular administration. In contrast to morphine, the onset is fast and duration of action is short.

With other opioids and CNS depressants it acts synergistically. Tolerance develops with repeated use. This leads to increase in the minimal effective dose. Over a few days, physical dependence develops. Side effects are nausea, vomiting, bradycardia, depression of respiration and chest wall rigidity (133–135).
They act synergistically with anesthetics and reduce dose requirement of anesthetic agents. It does not cause myocardial depression, so it is invaluable in LV dysfunction. It has definite cardio protective actions like antiarrhythmic activity especially in ischemic reperfusion injury. Due to its action on δ- and κ-opioid receptors there is prolongation of the cardiac action potential duration.(136)Remifentanil and fentanyl both induce preconditioning of the myocardium, even though their action at δ- and κ-opioid receptors are weak. Reducing the dose of anesthetic drugs is often the safest way to induce patients with LV dysfunction. Large doses of fentanyl as the only anesthetic have the advantage of stable hemodynamics, there is lack of direct depression on the myocardium, with no release of histamine and stress response to surgery is suppressed(137). There are no changes in the contractility of myocardium. After large doses of fentanyl, hemodynamic variables remained unchanged. Fentanyl may depress cardiac conduction by direct membrane actions.(138). During induction in patients undergoing CABG, QT interval was found to be prolonged. Conductance in coronary circulation is regulated by arterial baroreceptors. This is increased by low fentanyl concentration in plasma, but it is suppressed with high fentanyl plasma concentrations(139). Studies in dogs showed a direct peripheral vessel smooth muscle relaxation(140). Its antiarrhythmic potential, anti-ischemic action and action on opioid receptors was demonstrated in rabbits, (141)
In mitral valve surgery, Fentanyl was used as the only anesthetic in doses of 50-100 pg/kg. (STANLEX & WEBSTER 1978) and CABG (LUKN et al. 1979). The hemodynamic stability was good as there is lack of myocardial depressant effect. Fentanyl in dose of 50-70 pg/kg caused deep surgical anesthesia, as seen in EEG, no awareness was being reported. (SEBEL et al. 1981)

To achieve stability in hemodynamics, opioids in high dose and anesthetic agents in a low dose were used to suppress the response to surgery (Ruggeri et al., 2011). It did not cause depression of the myocardium (Howie et al., 2001; Rauf et al., 2005 and Steinlechner et al., 2007). However, opioids in increasing doses do not suppress the surgical stress response, the plane of anesthesia has to be modified (Howie et al., 2001).

In the myocardium, metabolism of phosphates was blocked in a study by VAN DEK VUSSE et al. (I 979) when ischemia was caused in dogs, and showed that it could be explained by the negative chronotropic effect of fentanyl. When high doses of fentanyl are used, metabolic and hormonal changes were decreased. During gynaecological surgery, there was a decrease in metabolic and hormonal changes as demonstrated by HALL et al. (1978). In the stage before bypass, it diminishes the endocrine and hyperglycemic response to surgical stimuli. During bypass, there was significant increase in catecholamines (SEBEL et al. 1981b). Similar study was done by STANLEY
et al. (1980). Stress response was higher when fentanyl was given in a low dose, with associated coagulopathy, and required more transfusion. Fentanyl at high doses were favorable in preventing stress response. There was better analgesia post operatively, when dexmedetomidine was added to fentanyl at low doses vs. low dose fentanyl, in preventing response to stress (142). It may cause prolongation of recovery due to respiratory depression, as it gets accumulated (Lison et al., 2007). In cardiac patients with high risk, Remifentanil has been used successfully (Lehmann et al., 1999). Recovery was rapid when remifentanil infusion was given for a long time (Ruggeri et al., 2011).

Midazolam at a dose of 0.075 mg/kg or 0.15 mg/kg IV along with high-dose fentanyl caused decrease in the mean arterial pressure by 24-32% from the baseline rapidly. Minor to moderate decreases in mean arterial pressure was observed when midazolam was used as the sole induction agent (143–145) along with low doses of fentanyl (144) in cardiac patients; peripheral vascular resistance decreases caused by the midazolam causing drop in BP (144). When high doses of midazolam more than 1 mg/kg are given, it has negative inotropic effects on the myocardium (146). Since the combination of midazolam and fentanyl caused significant hypotension, a loading dose of 3-5 mcg/kg was given during induction in our study, as hypotension is detrimental to patients with left ventricular dysfunction. When fentanyl is used as the sole anesthetic, the disadvantages are failure to prevent sympathetic
stress response, unpredictable amnestic effects leading to recall, and postoperative ventilatory depression.(147–149).

Fentanyl is available as transmucosal and transdermal forms. Intrathecal fentanyl in labor can produce good analgesia. Side effects include bradycardia, seizure-like activity, in head injury patients is associated with increase in ICP.(137)

**PROPOFOL**

It was developed at Imperial Industries in UK when the effect of phenol derivatives to cause sedation in animal models was discovered. In January 1973, its properties as an anesthetic agent were discovered(150,151). The chemical name is 2, 6-diisopropylphenol and the weight of a molecule is 178.27. At a pH of 6-8.5, the octanol and water partition coefficient is 6761. At a pKa of 11, the formulation is in an oil-in-water emulsion, which is white, as it is not soluble in water. All fat soluble anesthetic agents can be delivered, bacteria proliferate easily in that media. After contamination, there is risk of sepsis. It acts on GABA receptors(152). This was first observed by Collins et. al. in 1988 (153). The strong point of propofol is its fast onset and fast offset due to it’s short, context-sensitive half time. The onset of action is dose dependent 9-51 seconds, the peak effect is seen at 90-100 seconds. The initial t1/2 is 1-8 minutes, terminal t½ is 4-7 hrs. A dose of 2 - 2.5 mg/kg造成 systolic BP to drop by 25% -40% (154). Mean and diastolic blood pressure also falls which is due to vasodilation of the arterial system. There is
reduced vascular tone. It may also affect myocardial contractility and autonomic control of cardiac output (155). There is decrease in systemic vascular resistance in arteries and veins, so preload and afterload are reduced. The pulmonary arterial and capillary wedge pressure decrease in cases of valvular heart disease (156). The effect is more in hypovolemic patients and in the elderly.

It causes decrease in systemic blood pressure, decrease in sympathetic tone of vasculature, and decrease in SVR, with no effect on myocardial contractility. (157, 158). This explains the cardiovascular depression, revealed as a reduction in arterial blood pressure. Calcium is taken up into the sarcoplasm which explains the negative inotropy. At usual doses, the effect on myocardium is not significant. Propofol concentrations in blood decreased slower than thiopentone as the tissue and blood distribution coefficient was higher (5.94).

There is negative inotropic effect depending on dose. It causes decrease in preload of LV, afterload and stiffness of regional chambers, causes LV filling to be impaired.

It protects the myocardium against injury by ischemia and reperfusion. It inhibits KATP channels at 5-15 times high concentrations at that of clinically used concentrations.
It has a free-radical scavenging property similar to vitamin E as the structure is similar. Free oxygen radicals are scavenged, decreases disulfide bonds in proteins. In organelles it prevents lipid peroxidation caused by oxidative stress. Due to its antioxidant and free radical scavenging nature, it protects the myocardium, which was demonstrated in experiments. Propofol causes significant cerebral vasoconstriction according to the dose given. It causes cerebral blood flow to decrease, oxygen demand is decreased and any pre-existing cerebral edema is enhanced. It has no effect on cerebral auto regulation and cerebrovascular reactivity to CO2. It causes rise or fall in ICP, causing cerebral perfusion pressure to decrease. The induction dose of propofol of 1 - 3 mg/ kg. Apnea occurs in a few minutes. The apnea duration and its occurrence is affected by the speed and dose of injection and any premedicant given.

It is the drug of choice when rapid and complete awakening is desired. It is used in TIVA (total intravenous anaesthesia). It is used as continuous infusion for sedation in ICU. Other favorable effects are its antiemetic effects, antipruritic, and anticonvulsant actions. It also attenuates bronchoconstriction. It decreases ICP in patients with normal or raised ICP. Unfavorable effects are pain on injection, apnea, and hypotension. When propofol is given for 48 hours or longer at a rate of 4 mg/kg/hr, propofol infusion syndrome may occur.
THIOPENTONE

It is a barbiturate, supplied as a hygroscopic pale yellow powder. It is insoluble in water. It is available as a carbonate salt to maintain the alkaline pH. Even though it is 80% protein bound it is taken up into brain rapidly within 30 secs due to its lipophilic nature and non-ionised fraction of 60% which is high. Ampoules contain sodium thiopental (500 mg) in nitrogen atmosphere with 6% sodium carbonate. When 20 ml of water is added, 2.5% solution (25 mg/ml) is formed. It has a pH of 10.8. The solution is alkaline and kept for 48 hrs safely, it is also bacteriostatic. GABA action is enhanced, whereas it blocks the synaptic action of glutamate and acetyl choline. The onset of action is 10-30 secs, t1/2 is 4.6-8.5 minutes, peak effect is 30 secs, and duration of action is 10-30 minutes.

In the barbiturate ring, the sulphur at C2 is replaced by oxygen atom. It has a fast onset of action and terminal half-life is reduced from 30 ± 50 h to 10 ± 15 h, due to its chemical structure (Chan et al., 1985) It should be termed as RS-, (+/-). It is a racemate as equal concentrations of (+)-R- and (7)-S-enantiomers are present. In mice it was found that the hypnotic potential of S-thiopentone is more than R-thiopentone (Christensen & Lee 1973; Haley & Gidley 1976) (Market et al., 1977)

In volume depleted patients, or those who have low serum albumin, or when non-ionized fraction is increases as in metabolic acidosis, at a particular dose, concentrations in the brain and heart achieved were higher. There is risk
of cardiac depression. When a single dose given as bolus, it is distributed quickly to tissues with high perfusion and low volume like brain and spinal cord. It then redistributes to lean muscle tissue, then the effect of the induction dose ends. (202)

There was minimal depression of arterial pressure at 10, 15, 20 minutes (p<0.05). There were significant increases in cardiac output at 2, 5 minutes (p<0.01), there was decrease in total peripheral resistance at 2 and 5 minutes. With thiopental, heart rate changes were also significant at 2 minutes (p<0.001), 5 minutes (p<0.01), and at 10 and 15 minutes (p<0.05). There was a decrease in stroke volume at 2 minutes (p<0.01) and 5 minutes (p<0.05). The peripheral leg blood flow increased significantly at 2 and 5 minutes. (167)

It causes depression of the myocardium, due to medullary centre inhibition, causing mean arterial pressure (MAP) to decrease. The outflow of sympathetics decreases, causing capacitance vessels to dilate. Baroreceptors cause reflex sympathetic stimulation, elevation in heart rate occurs due to baroreceptor-mediated sympathetic reflex stimulation of the heart when BP or cardiac output decreases. These effects are seen clearly in hypovolemic patients, those on beta-blockers, and valvular heart disease and cardiac tamponade. It causes ventilatory centre in the medulla to get depressed and hypoxic and hypercapnic response decreases. It causes spasm of larynx or bronchi as airway reflexes are not suppressed fully. It has
analgesic properties. Cerebral metabolic oxygen consumption rate (CMRO2) decreases, cerebral blood flow and intracranial pressure also decrease. In EEG increased doses, cause burst suppression which may prevent ischemia of focal areas. (168)

It is used as a premedicant and in the induction of anesthesia. Prompt onset, and smooth induction are the benefits. In normovolemic patients it causes transient decrease in BP that is compensated by tachycardia. It causes dose-dependent depression of medullary ventilatory centres. It stimulates an increase in enzyme induction which may result in altered drug interactions. Intra-arterial injection causes intense vasoconstriction. It is also associated with allergic reactions.

The effects of thiopentone on eight patients who had CAD and normal ejection fraction were studied by Reiz et al. Thiopentone decreases myocardial oxygen consumption, caused a decrease in arterial pressure, SVR and SVI. (169)

**KETAMINE**

Ketamine is a phencyclidine derivative that produces dissociative anesthesia. It is soluble in water, has a pKa of 7.5. This enables it to be non-irritant drug in any route of administration. (170–175).
It is 10 times more lipophilic than thiopentone and therefore can cross the blood brain barrier. Due to rapid redistribution, ketamine has fast onset and offset, which is similar in action to thiobarbiturates. It is a noncompetitive NMDA antagonist. The onset of sedation was 45 seconds with intravenous injection in a dose of 2 mg/kg, and after i.m injection (3 mg/kg) was 4 minutes. The time for recovery was 18 mins with IV and 25 mins with IM injection. After intravenous injection, half-life of distribution was 24.1 seconds, half-life of redistribution was 4.68 minutes, and half-life due to elimination was 2.17 hours. Peak effect is seen within one minute of intravenous injection. Liver is where biotransformation occurs. However, one of the most important pathway involves cytochrome p450 enzyme system causes N-demethylation of ketamine to nor ketamine.

The induction dose is 1-2 mg/kg intravenously. It produces analgesia, induces significant (33%) increase in heart rate, mean arterial pressure (+28%) and epinephrine levels, there is centrally mediated sympathetic nervous stimulation.

There is uptake of catecholamines in the neurons, stimulation of the central sympathetic system. These effects are in contrast to the negative inotropy on the myocardium. In a healthy individual, increase in arterial blood pressure, heart rate, and cardiac output occurs.
In the absence of good myocardial function and sympathetic reserve, hypotension may occur due to myocardial depression.

Coronary blood flow may not be enough to meet the increased oxygen demands due to sympathetic stimulation.

In the presence of increased β-adrenergic stimulation, the failing heart cannot increase the contractility when given ketamine.(178). In such patients, there is decrease in cardiac performance and cardiovascular instability occurs. In the presence of adrenoceptor blockade, the negative inotropic effects may be unmasked.(179) Ketamine is a chiral compound, and until recently was only available as the racemic mixture.

The advantages of S (+)-ketamine at lower concentrations, is that it causes hypnosis and analgesia, agitated behavior and emergence delirium are less. This isomer depresses the myocardium to a lesser extent than its racemate.(180) The R (–) isomer, blocks ischemic preconditioning of the myocardium, S (+)-ketamine does not have this action. (181) In contrast, however, Hanouz et al (207) demonstrated that both isomers causes preconditioning of the myocardium. The mechanism involved is that Potassium ATP channels are activated, and α-, β- receptors are stimulated. It has some anticonvulsant activity due to its action on NMDA-receptors. Ketamine is both anticonvulsant and neuroprotective as shown by recent studies(182–184)
It is unique in the sense that, it induces intense analgesia at subanesthetic doses (0.2-0.5mg/kg), and causes prompt induction of anesthesia at higher doses. Analgesia can be produced in labor without neonatal depression. Due to its rapid onset of action, it has been used as an intramuscular injection drug in mentally challenged patients. In acutely hypovolemic patients, induction with ketamine is often done. However, it can be drastic in critically ill patients where catecholamine stores are depleted. In asthma patients it is useful, as it causes bronchodilation.

It causes emergence delirium. It causes sustained increase in ICP in patients with intracranial pathology. It inhibits platelet aggregation.

**MIDAZOLAM**

It is an imidobenzodiazepine derivative. It can be used as a premedicant, sedative and an induction agent. It has a fused imidazole ring, which is responsible for the basic nature, stability of an aqueous solution and for its rapid metabolism. The pKa of midazolam is 6.15. The onset of action is about 2 minutes. The distribution half-life is 6-15 minutes, elimination half-life is 1.7-3.5 hrs. Peak effect is 30-80 minutes, duration of action is 1-4 hours.

There is no irritation after IV injection. It becomes highly lipophilic at physiologic pH. It is one of the most lipid soluble of the benzodiazepines.
There is rapid entry of midazolam into the brain tissue. 96-97% is bound to plasma proteins. GABA chloride channels are opened causing hyperpolarization.

**Pharmacodynamics**

It causes anxiolysis, hypnosis, muscle relaxation and amnesia. It also has anticonvulsant action. It has affinity for glycine receptors in the brain, it increases the glycine inhibitory neurotransmitter, and thus it exerts anxiolytic effect. It has a high affinity for benzodiazepine receptor about 2 times that of diazepam and GABA accumulation occurs. GABA is accumulated because GABA reuptake is inhibited. Hypnosis is explained by the excess GABA at neuronal synapses.

It was found that the midazolam dose when used together with fentanyl was significantly lower than that in the other 2 groups, indicating that fentanyl enhanced the degree of sedation, and our results are similar to those of others. (185, 186)

It is effective in minimizing stress response to intubation

With a dose of 0.15 mg/kg it caused anesthesia while 0.5 mg/kg caused sedation. The induction dose is 0.05-0.15 mg/kg. Sedation dose is 0.5-1 mg which is repeated at intervals. An ideal induction agent is one which induces sleep in one arm-brain circulation time. Onset and duration of action varies.
Hence, it has a delayed onset of action which has the risk of over dosage. Due to its nonirritant and short acting nature, sedative doses of 0.05 mg/kg have been used during cardiac catheterization (122). For CABG, midazolam at low doses when combined (0.075 - 0.15 mg/kg) with fentanyl at high doses, 75 μg/kg causes systolic BP to drop by 29 to 33%, diastolic BP to drop by 30 to 31%. The stroke index decreases by 25 to 30%. The left and right ventricular stroke work index decrease by 42 to 46% and 48 to 61% respectively. This can be explained due to increased pooling of the venous system (124). The elimination is slowed with a half-life of 281 mins, after perfusion of the extracorporeal system. As the overall peripheral resistance decreases, it causes a significant reduction (2.2%) in the mean blood pressure. There is minimal cardiovascular and respiratory effects, there is smooth transition to inhalation anesthesia after sub anesthetic doses. There is almost total absence of excitatory effects. Patient acceptance is good, making it a good alternative to thiopental. The amnesic effect is more than double its respiratory depression properties (144). Generally, when compared with thiopentone, respiratory depression was less (144, 148).

It causes decrease in CMRO2 and cerebral blood flow similar to thiopentone and propofol. It is a potent anticonvulsant used for treating status epilepticus. It causes dose dependent decrease in ventilation by decreasing hypoxic drive. Studies done have shown it may have a role in prevention of post op nausea and vomiting (187). The most important side effect is respiratory depression.
The agents used during induction commonly in cardiac patients are diazepam and flunitrazepam because the effects on the cardiovascular system are minimal (Coleman et al in 1973; Cote, Gueret and Bourassa in 1974; Stanley et al.in 1976; Clarke and Lyons in1977; Tarnow et al.in1979; McCammon, Hilgenberg and Stoelting in1980)

In CAD patients 0.2 mg/kg of midazolam caused the MAP to decrease from 92-80 mm of Hg 5 mins after induction. Midazolam in a dose of 0.2 mg/kg was used and its effect on five CAD-patients who had low cardiac output, increased SVR and high filling pressures of the left ventricle was studied by Reves, Samuelson and Lewis in 1979.It caused a significant decrease of systemic vascular resistance (SVR). Thereby it allowed a significant improvement in pump function and a decrease in the increased left ventricular filling pressure. However midazolam did not prevent the intubation stress response.

Dose in elderly:In elderly, doses of 300 mcg/kg can be given over a time of 20-30 seconds initially; after 2 to 3 minutes, the effect of sedation is assessed and adjustments in dose are made. The dose used in Left ventricular dysfunction patients was 0.15-0.2 mg/kg(9)
**Metabolism:**

Midazolam is metabolized by hydroxylation through hepatic microsomal enzymes. The fused imidazole ring is oxidized by the liver rapidly, 1-hydroxy midazolam is the main metabolite, and 4-hydroxy midazolam are formed in small amounts. These are excreted in urine in the form of glucuronide conjugates.

Its rapid onset of action is explained by its high lipophilicity, equilibration between plasma and CSF occurs very rapidly. Due to rapid clearance and elimination it has a short duration of action.

The first phase of metabolism is due to the drug distribution. The second elimination phase is due to biotransformation. 50% blood flow in liver causes midazolam to get cleared fully. Distribution is wide and rapid elimination occurs. In elderly, volume of distribution is increased. Volume of distribution is larger in women than men.

**CLINICAL USES**

It produces sleep and amnesia but no analgesic effect. The induction dose is 0.1-0.4 mg/kg. A dose of 0.2 mg/kg can be given safely in high risk patients. 2 studies were done, White used 0.3mg/kg and induced anesthesia in 30-60 sec.(188) Finucaine gave the same amount in 4 incremental doses and took 4.9 minutes to induce(189). The elderly require a lower dose of midazolam. ASA 3 and 4 patients require less dose 0.15-0.2 mg/kg. Age >55 and ASA >3 patients require 20% less dose than young, fit patients.
In patients in pediatric age group, who had very low cardiac index, Fentanyl has a fast onset and changes in hemodynamics were minimal. However, when given along with benzodiazepines it can cause circulatory depression and requires volume expansion, and in some cases inotropic support. (190–193) Heart rate, BP and cardiac index were depressed, by fentanyl and midazolam combination in a study done by Revines et al (222). In children undergoing CABG, dexmedetomidine and fentanyl was compared with midazolam and fentanyl, was compared. The effect on cardiac output in both the arms could not be determined, even in the presence of similar SvO₂ at the recording moments (194). At one hour before surgical stimulus, HR and systolic blood pressure were reduced in both groups to a significant extent. However, midazolam recorded a significant response to surgical stress and required increased supplementation with isoflurane. With the use of Dexmedetomidine, analgesic effects was potentiated (195). The changes in hemodynamics were similar in both the arms.

Massaut et al. studied the effect in hemodynamics due to midazolam on eight anesthetized patients with CAD. Heart rate decreased by 9%, mean arterial pressure by 17%, CI by 9%, and SVR by 12%. They showed the effects on endocardial viability to be of benefit, and recommended the use of midazolam as an adjuvant to fentanyl anesthesia especially in patients with CAD. (169)
In chronic renal failure, anesthesia is induced more rapidly as there is more unbound drug to CNS receptors. Males are more sensitive to midazolam than females.

**Side effects:**

There is no nausea and vomiting. Since it is water soluble, there is low incidence of venous irritation and thrombophlebitis.

**ETOMIDATE**

It is not chemically related to any other drug. It contains an imidazole compound which is carboxylated. In 1965, it was first reported as one of the aryl alkyl imidazole-5-carboxylate esters. It was synthesized by Janssen Pharmaceuticals. During animal studies, the hypnotic action was observed. It has anti-fungal action. At physiologic pH it was lipid soluble, and at an acidic pH, it is soluble in water which is due to the imidazole compound. The original formulation included 35% propylene glycol which caused pain during injection. This was changed later to a fat emulsion. Myoclonus incidence is the same in both. Oral preparation has a higher blood concentration than intravenous preparation. Doenicke et al. have shown that the pain during injection was due to propylene glycol, a solubilizer. Pain and thrombophlebitis can be avoided, by using a lipid-emulsion formulation. Original preparation had high incidence of anaphylaxis which was avoided after they changed the preservative.
**Mechanism of action:**

There are several isomers of which the anesthetic effect is seen in the R+ isomer. It acts on the GABA receptor at specific sites and increases the affinity of GABA to these receptors.

**Pharmacokinetics:**

Onset of action is 30–60 seconds. Peak effect is seen at 1 minute. Duration of action is 3–5 minutes; the induction dose is 0.2-0.6 mg/kg. Volume of distribution is large hence there is considerable tissue uptake. After IV injection, in a time period of 1 minute, it reaches the peak effect due to rapid penetration into the brain. About 76% of the drug is bound to albumin independent of the drug concentration.

**Metabolism:**

The ethyl ester side chain is hydrolysed to carboxylic acid ester, resulting in a pharmacologically inactive compound. Hepatic enzymes and plasma esterases mediate this reaction. About 85% is seen as the carboxylic acid metabolite in urine and 10-13% as this metabolite in bile.

**Cardiopulmonary bypass:**

There is an initial decrease of 34% in plasma etomidate concentration, later it decrease to 11% of the prebypass value, there is a further decrease with rewarming.
Clinical uses:

In an unstable cardiovascular system etomidate is the drug of choice. Induction dose is 0.2-0.4 mg/kg. The onset of unconsciousness starts within one arm to brain circulation time. There is alteration in the balance between inhibitory and excitatory influences on the thalamocortical tract, hence involuntary myoclonic movements occur. By giving opioid before, this can be avoided. Awakening is more rapid compared with other barbiturates, there is no hangover effect. It does not have analgesic properties. After giving etomidate the return of psychomotor function is said to be intermediate to methohexital and thiopentone. It may also decrease the duration of seizures, it can be used as an alternate drug to propofol and thiopentone.

EFFECTS ON SYSTEMS

CNS:
CMRO2 (cerebral oxygen consumption rate) decreases by 35 to 45%, and cerebral blood flow is decreased due to vasoconstriction of cerebral vessels. Hence it decreases intracranial pressure. The pattern produced in EEG is similar to thiopentone, the frequency of excitatory spikes is more with etomidate.
**Cardiovascular system:**

Unlike other induction agents, it has fast onset and a safe cardiovascular profile, and hence causes less significant fall in blood pressure (196–198). The 30-day mortality and cardiovascular morbidity is increased with the use of etomidate, although hypotension during induction is prevented which can cause less perfusion of coronaries, arrhythmia, and cardiac arrest. There is also prolonged hospital stay.(199)

It has structural similarities to α2B agonists and results in vasoconstriction. This explains its hemodynamic stability. A patient with cardiovascular disease depends on the sympathetic tone for maintaining the blood pressure, systemic vascular resistance (SVR), and cardiac output. Etomidate by its action on α2B receptors negates the need for treatment of postinduction hypotension and is considered as an ideal induction agent in patients with cardiovascular compromise.(200)

The change in heart rate, cardiac output or stroke volume is minimal. There is no effect on the sympathetic nervous system or on the function of the baroreceptor. During induction it causes more hypertension and tachycardia than with the use of propofol. The myocardial oxygen supply to demand ratio is well maintained(177). Hence in acutely hypovolemic patients if etomidate is given, it can cause sudden hypotension due to parallel changes in SVR and
MAP. The only change which was observed was a 10% increase in heart rate, hence etomidate is considered to have a stable hemodynamic profile.

**RESPIRATORY SYSTEM:**

There is decrease in tidal volume with a compensatory increase in respiratory rate.

It may stimulate ventilation independently, hence it is useful when spontaneous ventilation is needed.

**Musculoskeletal**

Myoclonus occurs in 50-80% of the patients receiving etomidate. Giving fentanyl or benzodiazepine may reduce the occurrence of myoclonus. Giese et al. (202) reported that premedication with 100 μg fentanyl significantly decreased the rate of etomidate-induced myoclonus; however, it introduced the risk of respiratory depression. The mechanism of myoclonus is explained by disinhibition of subcortical structures that normally suppress extrapyramidal motor activity.
### Adrenocortical suppression

In the adrenal cortex etomidate inhibits 11-beta-hydroxylase, which is an enzyme which converts cholesterol to cortisol. It causes reversible inhibition in a dose dependent manner. 11–beta-hydroxylase plays an important role in adrenal steroid production leading to primary adrenal suppression (203). Using a continuous infusion may cause mortality(204). Patients with sepsis and hemorrhage are at a disadvantage because the intact cortisol response is disrupted. However, at clinical doses, the adrenal suppression caused due to single dose of etomidate is controversial as negative outcome data which can be conclusive are absent. (200). Iribarren looked at the incidence and impact of this adrenal suppression in 120 cardiac surgical patients. The overall incidence of adrenal suppression was 77% and 88% in the etomidate group.(4) The
patients in etomidate group who developed adrenal suppression received higher
doses and longer duration of inotropic support postoperatively. The duration of
adrenal suppression can last between 12–72 hours. The inflammatory response
is stimulated after cardiac surgery, during bypass surgery, level of
catecholamine and stress hormones are elevated (205). Cortisol and
corticosterone which are endogenous cytokines have a role in the maintaining
the vascular tone and nitric oxide production is inhibited. Since it acts
synchronously with epinephrine and norepinephrine in maintaining BP, these
hormones are impaired due to etomidate. During the postoperative period, there
is an increased vasopressors requirement (205)

In critically ill who have adrenal suppression CORTICUS trial showed
that exogenous hydrocortisone did not improve the survival (200)
The cortisol suppression caused by a single dose of etomidate is always limited
to 24 hours, there is no threat of prolonged adrenocortical suppression. In this
study the cortisol levels returned to normal levels at twenty-four hours post
induction (206). The benefit of minimal cardiac suppression is weighed against
causing adrenocortical suppression and longer hospital stay. The risk for 30-
day mortality, cardiovascular morbidity, and prolonged hospital stay were
increased (207)

RCT done showed that one group was assigned to receive etomidate 0.3
mg/kg (n=328) the other group ketamine 2 mg/kg (n=327) for induction. It was
found that adrenal insufficiency was significantly more in the etomidate group
than in the ketamine group (208)
The ideal induction agent

The ideal induction agent obtunds the intubation stress response and also maintains hemodynamic stability. The properties of an ideal induction agent are as follows:

Physical properties

• It should be water soluble & stable in solution and stable on exposure to light.
• It should have a long shelf life with no pain on intravenous injection.
• It should be painful when injected into an artery and non-irritant when injected subcutaneously. There should be a low incidence of thrombophlebitis and it should be cheap.

Pharmacokinetic properties

It should have a rapid onset in one arm-brain circulation time, rapid redistribution to vessel rich tissue. It should have rapid clearance and metabolism with no active metabolites.

Pharmacodynamic properties

• It should have a high therapeutic ratio (ratio of toxic dose: minimally effective dose) with minimal cardiovascular and respiratory effects.
• There should be no histamine release/hypersensitivity reactions, no emetic effects.
• There should be no involuntary movements and no emergence nightmares.
• There should be no hang over effect, no adrenocortical suppression.
• It should be safe to use in porphyria.

Patients with impaired left ventricular function are at a high risk for any cardiac surgery. Etomidate is well known to have a stable cardiovascular profile. Other conventional techniques like using high dose fentanyl or midazolam with fentanyl normal dose have also been used during induction. A RCT done in AIIMS compared four induction agents: etomidate, propofol, thiopentone and midazolam. The hemodynamic variables were comparable in all the four groups. Etomidate was not that effective while midazolam was the most effective in preventing stress response to intubation among the induction agents. Among the four groups, there was a comparable decrease in hemodynamic parameters. This can be explained by the hypothesis that during induction sympathetic stimulation is lost, it cannot be attributed to anesthetic induction agents. Etomidate was the most cardio stable drug, its effect on adrenal suppression was not studied.

**Hemodynamic effects of various intravenous induction agents in patients with normal LV function**

The magnitude of hypotension is directly proportional to the plasma concentration of the induction agent. The concentration depends on many factors like age, sex, dose and body weight, cardiac output and infusion rate. There is no agreement on the minimum dose of propofol and the method of
administering which minimizes hypotension risk. The dose of etomidate utilized by various studies ranges from 0.2 to 0.45 mg/kg. The doses at the higher end of the spectrum (0.4 mg/kg) for etomidate may cause direct myocardial depression(209). The exact induction dose of etomidate for maintaining hemodynamic stability has not been zeroed upon as yet. The magnitude of variations in SBP, DBP and MAP from baseline was greater when propofol was used as an induction agent versus etomidate in comparable doses. The mechanisms of arterial hypotension following IV anesthetic induction are multifactorial. There is no effect on the sympathetic nervous system, or the function of baroreceptors, this explains the safe cardiovascular profile. (209,210) It has the ability to bind and stimulate alpha-2B adrenergic peripheral receptors causing vasoconstriction.(211). Decrease in systemic blood pressure after a bolus injection of propofol is dependent on both vasodilation with reduced preload and afterload and myocardial depression (negative inotropic action).(209,212–214). It was demonstrated that ketamine, used as the anesthetic induction agent during high-dose remifentanil administration, might prevent cardiovascular depression. The choice of ketamine as the induction agent during high-dose remifentanil administration might be a safer alternative to propofol in patients in whom cardio-vascular depression needs to be avoided.(215)

Thiopentone, causes an increase in heart rate(216,217) but in infants there was no change at lower doses (217,218) and in the elderly there
was a decrease in heart rate (219). Direct effects on the myocardium explains the cardiac depression by propofol or thiopentone (220, 221). It has indirect action on the neuronal system (222). Many studies have reported depression of myocardium in a dose-related manner (220, 221, 223). There are a very few studies on the comparison of depressive effect on the myocardium by thiopentone versus propofol during induction (216–218). After induction with thiopentone, there was fractional shortening which decreased by 14%, there was no change with propofol. Gauss et al. (243), Mulier et al. (244) found that propofol group had significant cardiac depression than equal doses of thiopentone given as a single bolus. Left ventricular volume was measured using Transesophageal echocardiography intraoperatively.

Glissen et al. (224) studied the effects of propofol, thiopentone and etomidate. At clinical concentrations, etomidate did not have any effect on contractility of myocardium. Thiopental, however had a significant negative inotropic effect. Haris et al. (225) studied thiopental in a dose of 4 mg/kg, etomidate in a dose of 0.3 mg/kg and propofol in a dose of 2.5 mg/kg along with 2 µg/kg fentanyl in tracheal intubation. In the propofol group, there was a decrease in SAP, in the group which received only thiopentone and etomidate after intubation, SAP was found to be increased. Vohra et al. compared the stress response to intubation with thiopentone in a dose of 5 mg/kg, and propofol 3 mg/kg along with fentanyl 1.5 mcg/kg. (226). The cardiac output were measured using thoracic impedance in order to evaluate the hemodynamic
responses to intubation. There was no significant difference in the heart rate after induction, but in both groups there was a statistically significant increase in heart rate after intubation (p<0.01). After induction and intubation there was a significant decrease in cardiac output.

Pandey et al, did a study (227) comparing the effects of etomidate and propofol on hemodynamics and serum cortisol in patients undergoing CABG with normal left ventricular function. It was demonstrated that compared with propofol, etomidate offers hemodynamic stability during induction of anesthesia.

Studies done on patients with LV dysfunction

In a study done in AIIMS which compared induction agents in patients with coronary artery disease and left ventricular dysfunction, in all four groups, the hemodynamic response was similar. Variable changes in systemic vascular resistance was noted at induction and intubation, however the stroke volume variation and central venous pressure showed no significant changes. In preventing the stress response to intubation, midazolam was most effective, as evidenced by increase in heart rate by 4%, (p=0.12), MAP decreased by 1%(p=0.77). In the etomidate group, it was the least effective in preventing stress response. Heart rate (P = 0.001) and mean arterial pressure (P = 0.001) increased at 1 minute after intubation. All the four induction agents were suitable and can be used for induction in patients with coronary artery disease and left ventricular dysfunction, though cardiac index decreased by 30 to 40%
In such patients with left ventricular dysfunction, experience of clinician along with knowledge of the interactions (concomitant opioid use and premedication) is needed to achieve hemodynamic stability.

Etomidate which is used during anesthetic induction during cardiac surgery which includes CABG, has the least side effects on respiratory and cardiovascular functions, release of histamine was minimal, especially in patients with cardiac compromise (228). However, several studies suggest an association between etomidate administration, adrenal insufficiency and increased mortality in patients undergoing cardiac surgery (229, 230). Etomidate reversibly inhibits 11-beta-hydroxylase, an important enzyme in steroid production in adrenal cortex, which can lead to primary adrenal suppression (231). Etomidate blunts the HPA axis responses. HPA axis is activated as a body’s mechanism for adapting to illness and stress, which forms a component in maintaining the homeostasis of cells and organs (229).

Morel et al., (256) did a study comparing propofol or etomidate use during induction, the requirement of norepinephrine use during first 48 hours after cardiac surgery, the results show that with a single bolus of etomidate the HPA axis response was blunted lasting more than 24 hours, however requirement of vasopressors were not increased. They concluded that due to its significant inhibition of the HPA axis, etomidate should be used carefully in cardiac patients with high risk.

Another study found no difference in hemodynamic variable such as SAP, DAP, MAP and HR after induction of anesthesia and intubation with
etomidate versus ketamine-thiopental sodium combination between two groups. Due to these results we can consider the combination of ketamine and thiopental for anesthetic induction in CABG surgery patients with low EF (232)
MATERIALS AND METHODS

STUDY SETTING:

The study was conducted in the cardiothoracic operating theaters and cardiothoracic intensive care units in Christian Medical College Hospital, Vellore.

Study population:

49 consenting patients between 14-75 years who underwent cardiac surgeries during the 6 month study period in Christian Medical College Hospital, Vellore.

Inclusion criteria

Patients who were scheduled for coronary artery bypass grafting who have ejection fraction between 30- 45% were approached and those who were willing to participate were included in the study.

Exclusion criteria

- associated valvular heart disease,
- congestive cardiac failure
- on mechanical ventilation
- severe systemic non-cardiac disease
- known adrenal insufficiency
- on chronic steroid use
**Study period**

It was conducted over a period of 6 months between January to September 2016.

**Sample size**

A RCT done in AIIMS compared four induction agents etomidate, propofol, thiopentone and midazolam. The hemodynamic response was comparable in all four groups. Hemodynamic parameters were recorded starting from induction at 1 minute intervals till 7 minutes after intubation. Baseline Mean arterial pressure and every minute after induction the MAP was recorded. The MAP after 3-minute induction in the etomidate group was 75.3 and MAP in the midazolam group was 68.7.

With expected mean BP 75.3 (SD 10.7) in etomidate group and mean BP 68.7 (SD 9.2) in the midazolam group the minimum required sample for the study is 36 in each arm.
Two means- Hypothesis testing for two means

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th></th>
<th>II</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard deviation in</td>
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<td>11.7</td>
<td>10.7</td>
<td>10.7</td>
<td>7.1</td>
<td>7.1</td>
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<td>I</td>
<td></td>
<td>II</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Standard deviation in</td>
<td>16.2</td>
<td>16.2</td>
<td>9.2</td>
<td>9.2</td>
<td>11.1</td>
<td>11.1</td>
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<tr>
<td>group</td>
<td>II</td>
<td></td>
<td>II</td>
<td></td>
<td></td>
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<tr>
<td>Mean difference</td>
<td>14</td>
<td>14</td>
<td>6.6</td>
<td>6.6</td>
<td>8</td>
<td>8</td>
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<tr>
<td>Effect size</td>
<td>1.003584229</td>
<td>1.003584</td>
<td>0.663317</td>
<td>0.663317</td>
<td>0.879121</td>
<td>0.879121</td>
</tr>
<tr>
<td>Alpha error (%)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Power (1- beta) %</td>
<td>80</td>
<td>90</td>
<td>80</td>
<td>90</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>1 or 2 sided</td>
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<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Required sample size per</td>
<td>16</td>
<td>21</td>
<td>36</td>
<td>48</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>group</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

The sample size calculation using the Mean BP after 3 minute induction and standard deviation in each group was 72 using power of 80 and I have chosen the sample size as 72 with 36 in each arm.

Selection of study patient:

Prior permission was obtained from the institutional review board and the ethics committee to conduct the study. Patients who were electively planned for cardiac surgery and with a low ejection fraction were given the patient information sheet in the OPD. The primary investigator visited them the day before surgery and explained about the study. Patients who gave consent and fulfilled the inclusion criteria were included in the study and were allocated into either of the group, by random allocation.
Methodology

49 patients with moderate to severe left ventricular dysfunction, ejection fraction 30-45% were randomly assigned to two groups after informed consent. Patients who were scheduled for elective CABG were only included in the study. Exclusion criteria were patients with persistent arrhythmias, associated valvular heart disease, congestive cardiac failure, emergency surgery, on mechanical ventilation, known adrenal insufficiency, renal disease, history of steroid use in the preceding six months, and those with severe systemic non-cardiac disease, other than diabetes and hypertension. Patients with critical left main coronary disease and severe left ventricular dysfunction (Ejection fraction (EF) <30%) were also excluded from the study. On the day of surgery patients were premedicated with lorazepam 2 mg orally two hours prior to the procedure. Base line monitoring was established with pulse-oximetry, invasive blood pressure, and five lead ECG. Baseline heart rate (HR), systolic BP, Diastolic BP, Mean BP and ST segment at 0 (Before induction) were documented. Patients were randomized to the groups with computer based random allocation as sealed envelopes. The consultant anesthetist who anesthetize the patient used a drug according to the randomization. The variables like HR, SBP, MAP, DBP, ST segment, PPV were analyzed and documented at 1 minute after induction, 1 minute after intubation, 3 minutes after intubation and 5 minutes after intubation. Any rise or fall within 20% of base line or a MAP < 60 mmHg is considered significant. As we are
monitoring this continuously we will treat it aggressively if the values go beyond 20%.

Hypotension will be treated with Phenylephrine, ephedrine or noradrenaline infusion and hypertensive response will be treated with addition of fentanyl/sevoflurane (to increase the depth of anesthesia).

Baseline data like Heart rate, ST segment analysis in lead II and V5, Systolic Diastolic and Mean arterial pressure and pulse pressure variation (PPV) were measured. The patients were preoxygenated and received either etomidate or midazolam over a period of 60-90 seconds. Fentanyl a dose up to 3-5 mcg/kg was given during induction in both groups. Titrated doses of Etomidate (0.2-0.3 mg/kg) was given over 60-90 seconds in group A patients. Titrated doses of Midazolam (0.05-0.1 mg/kg) was given over 60-90 seconds in group B patients. Sevoflurane was used to induce and maintain 1MAC end tidal anesthetic agent concentration. Rocuronium (1mg/kg) will be used as the muscle relaxant to facilitate tracheal intubation. The patients were ventilated by bag and mask with oxygen and sevoflurane 2%. Heart rate, ST, systolic, diastolic and mean arterial pressure, and PPV were recorded before induction of anesthesia, every minute after induction till intubation, one, three, and five minutes after intubation. The first sample for serum cortisol levels was measured at 8:00 AM on the day of surgery, the second sample after protamine reversal (during C-sample) and the last sample at an interval of 24 hours after
the first sample (the next day 8:00 am). Hemodynamic variables were also measured at the times stated above. The range for serum cortisol at 8:00 AM is 5-25 microgram/dl. The study aims to see whether etomidate causes cortisol suppression. The data was analyzed to determine which drug is more hemodynamically stable during cardiac induction and intubation. Secondary outcomes like ICU days, Hospital days and any morbidity and mortality were also analyzed.
Detailed Diagrammatic Algorithm of the study

Patients who are electively planned for CABG based on inclusion and exclusion criteria

Preoperative informed consent

Baseline hemodynamic parameters are recorded

Patient will receive either etomidate or midazolam during induction (by double blinding)

Hemodynamic variables will be measured at one minute intervals from induction till five minutes post intubation

Comparison of hemodynamic response after intubation
Data analysed to determine which drug is hemodynamically stable
Methods

The agent used in cardiac surgery induction will be etomidate or other conventional techniques like fentanyl and midazolam. Both the groups were compared for their hemodynamic variables. The data was analysed to determine which drug is more hemodynamically stable.

ii. Key Criteria

a. Inclusion Criteria: Patients who were electively planned for coronary artery bypass grafting who have ejection fraction between 30-45% will be included in the study.

b. Exclusion Criteria: Patients with associated valvular heart disease, congestive cardiac failure, on mechanical ventilation, severe systemic non-cardiac disease and known adrenal insufficiency will be excluded from the study.

iii. Method of randomization: Random blocks will be generated and the patient will be allocated to either arm by randomly allocating based on the blocks.

iv. Method of allocation concealment: The allocation is concealed using sealed envelope technique.

v. Blinding and masking: The investigator who collects the data will be blinded to the drug. The anesthesia sheets will be marked as either drug A or B.
ANALYSIS

RESULTS

Baseline characteristics expressed as mean +/- SD

<table>
<thead>
<tr>
<th></th>
<th>Etomidate n=22</th>
<th>Midazolam n=27</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.36 +/- 9</td>
<td>56.37 +/- 9.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 22</td>
<td>Male 26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female 0</td>
<td>Female 1</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>63.86 +/- 8.49</td>
<td>65.04 +/- 9.0</td>
<td>0.36</td>
</tr>
<tr>
<td>Height</td>
<td>161.90 +/- 4.6</td>
<td>163.15 +/- 7.5</td>
<td>0.5</td>
</tr>
<tr>
<td>EF</td>
<td>42.38 +/- 2.9</td>
<td>41.6 +/- 3.6</td>
<td>0.42</td>
</tr>
<tr>
<td>Drug treatment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td>95.5</td>
<td>100</td>
<td>0.45</td>
</tr>
<tr>
<td>CCB</td>
<td>0</td>
<td>3.7</td>
<td>1.0</td>
</tr>
<tr>
<td>ACEI</td>
<td>36.4</td>
<td>22.2</td>
<td>0.35</td>
</tr>
<tr>
<td>ARB</td>
<td>13.6</td>
<td>14.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>46.4</td>
<td>53.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>47.8</td>
<td>52.2</td>
<td>0.78</td>
</tr>
<tr>
<td>Induction dose</td>
<td>0.2 mg/kg</td>
<td>0.04 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

The baseline characters were comparable in both the groups.
This chart shows the age distribution among the patients.

P value = 0.42
Out of 23 patients with hypertension 11 received drug A, 12 received drug B

Out of 28 patients with diabetes 13 received drug A, 15 received drug B
Hemodynamic response (MAP) to induction and intubation

<table>
<thead>
<tr>
<th>Time Points</th>
<th>Etomidate</th>
<th>Midazolam</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP baseline</td>
<td>102.91</td>
<td>97.15</td>
<td>0.24</td>
</tr>
<tr>
<td>1 min after induction</td>
<td>93.77</td>
<td>91.63</td>
<td>0.70</td>
</tr>
<tr>
<td>1 min after intubation</td>
<td>87.23</td>
<td>74.26</td>
<td>0.02</td>
</tr>
<tr>
<td>3 min after intubation</td>
<td>90.14</td>
<td>83.78</td>
<td>0.35</td>
</tr>
<tr>
<td>5 min after intubation</td>
<td>83.5</td>
<td>85.22</td>
<td>0.78</td>
</tr>
</tbody>
</table>

This shows that Etomidate is more hemodynamically stable than Midazolam, hypotension is more in the midazolam group. Hemodynamic response to intubation was similar between the groups.
**Hemodynamic response (HR) to induction and intubation**

<table>
<thead>
<tr>
<th></th>
<th>Etomidate</th>
<th>Midazolam</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR baseline</td>
<td>73.73</td>
<td>77.48</td>
<td>0.24</td>
</tr>
<tr>
<td>1 min after induction</td>
<td>72.32</td>
<td>76.74</td>
<td>0.22</td>
</tr>
<tr>
<td>1 min after intubation</td>
<td>76.68</td>
<td>75.44</td>
<td>0.78</td>
</tr>
<tr>
<td>3 min after intubation</td>
<td>78.27</td>
<td>79.26</td>
<td>0.83</td>
</tr>
<tr>
<td>5 min after intubation</td>
<td>73.05</td>
<td>77.15</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Both Etomidate and Midazolam cause a rise in heart rate after intubation, there is no significant difference between the two groups (p=0.83)
Hemodynamic stability at induction

<table>
<thead>
<tr>
<th></th>
<th>MAP baseline</th>
<th>at induction</th>
<th>1 min after induction</th>
<th>2 min after induction</th>
<th>3 min after induction</th>
<th>at intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>97.15</td>
<td>98.41</td>
<td>91.53</td>
<td>86.48</td>
<td>78.41</td>
<td>75.3</td>
</tr>
<tr>
<td>Etomidate</td>
<td>102.91</td>
<td>97.55</td>
<td>93.77</td>
<td>85.68</td>
<td>86.2/</td>
<td>81.2/</td>
</tr>
</tbody>
</table>

Requirement of Phenylephrine/Ephedrine/Noradrenaline

<table>
<thead>
<tr>
<th></th>
<th>Etomidate</th>
<th>Midazolam</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine (mg)</td>
<td>10.29</td>
<td>12.44</td>
<td>0.17</td>
</tr>
<tr>
<td>Phenylephrine (mcg)</td>
<td>117.65</td>
<td>160.0</td>
<td>0.27</td>
</tr>
<tr>
<td>Noradrenaline (mcg)</td>
<td>4.0</td>
<td>17.8</td>
<td>0.11</td>
</tr>
</tbody>
</table>

The requirement of Phenylephrine, Ephedrine and Noradrenaline was more in the Midazolam group. There was no significant difference between the two groups.
Stress response to intubation

Hemodynamic response to intubation was comparable between the groups.
Serum cortisol level

It can be seen that first sample at induction, in both the groups it is within normal values, but the baseline values were higher in the etomidate group. (The baseline was comparable. P=0.46) Etomidate causes suppression of cortisol values, hence after weaning from CPB, the C sample shows a decline in Etomidate group ,not in the midazolam group.(p value=0.001) The third sample value is higher in the etomidate than midazolam group. The value is reaching near normal in the midazolam group.

Serum cortisol values

<table>
<thead>
<tr>
<th></th>
<th>At induction</th>
<th>C sample</th>
<th>24 hrs after first sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate</td>
<td>17.22</td>
<td>10.16</td>
<td>29.84</td>
</tr>
<tr>
<td>Midazolam</td>
<td>15.73</td>
<td>17.21</td>
<td>25.8</td>
</tr>
</tbody>
</table>

mcg per dl

- Serum Cortisol
CK – MB levels

CKMB values post–op show a declining trend in both the groups.
Vasoactive inotrope score

Vasoactive inotrope score

![](image)

![Chart showing Vasoactive Inotrope Score comparison between Lomidate and Midazolam.](chart)

\[ p = 0.21 \]

VIS was calculated using the following over 24 hours:

**Ionotrope score (IS)** = Dopamine dose (mcg/kg/min) + Dobutamine dose (mcg/kg/min) + 100x Adrenaline dose (mcg/kg/min)

**Vasoactive Ionotrope score** = IS + 10x Milrinone dose (mcg/kg/min) + 10000 x Vasopressin dose (units/kg/min) + 100x Noradrenaline dose (mcg/kg/min)

Though there were concerns over adrenal suppression by etomidate, hence requiring vasopressors postoperatively, the above bar diagram shows that midazolam group has recorded a higher ionotrope score.
Number of ICU days

![Number of ICU days chart](chart1)

\[ \text{Number of ICU days} \]

\[ p = 0.02 \]

Number of hospital days

![Number of hospital days chart](chart2)

\[ \text{Number of hospital days} \]

\[ p = 0.25 \]
There was a negative correlation seen between EF and PPV. As the EF decreases, the PPV was found to be rising.

41.4% of patients had PPV > 12 and hypotension (>20% drop in BP from baseline)
38.3% of patients (among second cases) had hypotension which was similar in the other group (36.5%), in evaluating the role of NPO status in hypotension.
The above graphs show the relation between ST changes and hypotension.

There were no reported incidents of pain on injection, phlebitis or myoclonus with the use of etomidate.
Incidence of significant hypotension

<table>
<thead>
<tr>
<th></th>
<th>Etomidate (n=22)</th>
<th>Midazolam (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>7 (31.8%)</td>
<td>14 (51.85%)</td>
</tr>
</tbody>
</table>

p=0.88

The number of patients who had MAP less than 60 at any point of time during induction among the two groups were compared. 51.85% patients in the midazolam developed significant hypotension compared to only 31.8% in the etomidate group. (p value between the 2 groups=0.88)
49 patients were assigned to two groups, etomidate or midazolam, based on random allocation. Baseline demographic characteristics were comparable between the two groups. The study was conducted in patients with mild to moderate LV dysfunction. However, the mean EF was 42.38+/−2.9 vs. 41.6+/−3.6 in the etomidate and midazolam groups respectively, which qualifies as mild LV dysfunction.

Etomidate was more hemodynamically stable as seen by the serial MAP values which were consistently not less than 20% of baseline in the etomidate group. There was significant difference in the MAP value 1 minute after intubation. Our results were comparable to studies which have shown etomidate to have a safe cardiovascular profile by Gooding et al., Sun (1991), Yunqi et al., Hosten et al., and Pandey et al. The number of patients who had MAP less than 60 at any point of time during induction among the two groups was compared. 51.85% patients in the midazolam developed significant hypotension compared to only 31.8% in the etomidate group. (p value=0.88). However, we didn’t measure the duration of significant hypotension (MAP <60 mmHg) which is a drawback of the study. Any blood pressure less than 20% of the baseline was treated with pressors and if needed noradrenaline. The patients in the midazolam group received more ephedrine, phenylephrine and noradrenaline. Even though the difference is not statistically significant, it indirectly indicates the increased incidence of hypotension in the midazolam group.
In patients who are to undergo CABG, using fentanyl in high doses is an established technique in anesthesia.(148,233,234). The advantage is that there is minimal disturbances in hemodynamics, even in patients with poor left ventricular function. (149). But fentanyl in high doses is not sufficient to blunt the stress response by intubation and additional sedation is required to cause amnesia(235,236). However, a combination of midazolam and fentanyl are known to result in significant hypotension. In the era of fast tracking, the use of high dose fentanyl is almost obsolete as it can result in delayed extubations. We decided to use 0.05 -0.1 mg/kg of midazolam, but most consultants who gave anesthesia erred on the side of caution and the average dose of midazolam administered was 0.04 mg/kg. 43% of patients were more than 60 year old and the anesthetist would have accounted for the age for dose reduction.

Hemodynamic response to intubation were comparable between the groups. Both groups suppressed the laryngoscopic response to intubations effectively. Our findings are in contrast to Singh etal who found that midazolam was more effective than etomidate in prevention of hemodynamic response to intubation. We agree with him in his hypothesis that most of the hemodynamic changes are attributable to the loss of sympathetic stimulation on induction rather than to anesthetic drugs per se.
It can be seen that the first sample of serum cortisol at induction, in both the groups is within normal values, but the baseline values were higher in the etomidate group. (The baseline was comparable. $P=0.46$) The C sample shows a decline in serum cortisol level in Etomidate group but not in the midazolam group. ($p$ value=0.001). However the values are within normal limits. The third sample value is higher in the etomidate than midazolam group.

In both the groups, third sample 24 hour value were higher as compared to baseline values. Hence it can be seen that the adrenal suppression caused by Etomidate did not last more than 24 hours. Also the clinical significance of this suppression is not clear. Our results are comparable to Zurick et al who showed that Etomidate caused suppression of serum cortisol levels after even a single dose, leading to cortisol reduction lasting up to twenty-four hours (206).

The inotrope score ICU stay and hospital stay were less in etomidate group compared to midazolam group. The ICU stay in the etomidate group was found to be significantly less in the etomidate group. Our results are in contrast to CORTICUS trial and other trials done in ICU patients and septic patients (230) showing an increased inotropic requirement, morbidity and mortality in etomidate group. However our population is different. We agree with A.M Zurick et al who concluded that the cortisol suppression caused by a single dose of etomidate is mostly limited to 24 hour period (206), there is no threat of prolonged adrenocortical suppression. Our data is in agreement with Morel.
al who concluded that a single bolus of etomidate causes the hypothalamic–pituitary–adrenal axis response to be blunted for more than 24 h in patients who are to undergo elective cardiac surgery, but this was not associated with an increase in requirement of vasopressors (229). However our sample size is not complete to reach a conclusion. Our results contrasted with Iribarren et al who found that the use of etomidate in elective CABG cases was associated with relative adrenal insufficiency and increasing requirement of vasopressors postoperatively (230). Our study showed a reduced inotropic requirement and ICU stay in etomidate group. Our results contrasted Iribarren who did a study in 120 cardiac patients and found that a single dose of etomidate resulted in 12-72 hours of adrenal suppression.

In our study there were no reported incidents of pain on injection, phlebitis or myoclonus with the use of Etomidate. None of the patients developed stroke, renal failure, and myocardial injury. There were 2 cases of mortality during the study period.

We couldn’t find any significant ST segment changes during induction or intubation.

We could not derive any meaningful association between PPV and hypotension. This is partly because we did not fulfill the prerequisite for measuring PPV that the patient should be mechanically ventilated.
LIMITATIONS OF THE STUDY

We did not complete the required sample size. So the study is underpowered to reach any conclusions.

Duration of hypotension was not documented.

We didn’t analyze the multivariate predictors of hypotension as we didn’t complete the sample size.

We didn’t use a pulmonary artery catheter which would have showed us the changes in cardiac output, stroke volume and systemic vascular resistance. Even though these data would have added to the value of the study we didn’t find a favorable risk benefit ratio as most of our patients had only mild LV dysfunction.
Conclusion

1. Etomidate offered significantly better hemodynamic stability compared to midazolam for induction of anesthesia in coronary artery disease patients with mild left ventricular dysfunction.

2. Etomidate was comparable to midazolam in suppressing hemodynamic response to intubation in the study population.

3. Even though etomidate suppressed the immediate stress response to surgery, the serum cortisol levels were within normal limits and reached a comparable value by 24 hours. Also the inotrope score, ICU stay and hospital stay were better in etomidate group indicating that the adrenal suppression is not clinically significant.
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ANNEXURES