"COMPARISON OF EFFECTS OF GENERAL ANAESTHESIA INDUCTION

WITH

THIOPENTONE-FENTANYL AND PROPOFOL-FENTANYL COMBINATIONS

ON

LEFT VENTRICULAR SYSTOLIC FUNCTION ASSESSED BY TRANS-THORACIC ECHOCARDIOGRAPHY:

A ONE YEAR RANDOMISED CLINICAL TRIAL"

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"COMPARISON OF EFFECTS OF GENERAL ANAESTHESIA INDUCTION WITH THIOPENTONE-FENTANYL AND PROPOFOL-FENTANYL COMBINATIONS ON LEFT VENTRICULAR FUNCTION ASSESSED BY TRANSTHORACIC ECHOCARDIOGRAPHY : A ONE YEAR RANDOMISED CLINICAL TRIAL"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

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LIST OF ABBREVATIONS

2D	2 Dimensional
ABW	Adjusted Body Weight
ACTH	Adreno Cortico Tropic Hormone
ASA	American Society of Anaesthesiologists
ATP	Adenosine Tri-Phosphate
AV	Atrio-Ventricular
BBB	Blood Brain Barrier
BP	Blood Pressure
CBF	Cerebral Blood Flow
cm	Centimeters
cMRI	Cardiac Magnetic Resonance Imaging
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
CNS	Central Nervous System
CO	Cardiac Output
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal Fluid
CVS	Cardiovascular System
DBP	Diastolic Blood Pressure
ECC	Excitation Contraction Coupling
ECG	Electrocardiography
EDTA	Ethylenediamine Tetra acetic Acid
EDV	End Diastolic Volume
EEG	Electroencephalogram

ESV	End Systolic Volume
$EtCO_2$	End Tidal Carbon dioxide
FRC	Functional Residual Capacity
GA	General Anaesthesia
GABA	Gamma Amino Butyric Acid
HR	Heart Rate
ICP	Intracranial Pressure
ICUs	Intensive Care Units
IV	Intra Venous
LA	Left Atrium
LAD	Left Anterior Descending
LCx	Left Circumflex
LV	Left Ventricle
LVEDD	Left Ventricular End Diastolic Diameter
LVeDP	Left Ventricular End Diastolic Pressure
LVeDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End Systolic Diameter
LVESV	Left Ventricular End Systolic Volume
LVFS	Left Ventricular Fractional Shortening
MAP	Mean Arterial Pressure
MAX	Maximum
MCHAD	Medium Chain Acyl Co-Enzyme A Deficiency
MCL	Mid Clavicular Line
MIN	Minimum

mmHg	Millimetres of Mercury
NCX	Sodium Calcium Exchange
NIBP	Non-Invasive Blood Pressure
NMDA	N-Methyl d-Aspartate
PLAX	Parasternal Long Axis
PONV	Postoperative Nausea and Vomiting
PPV	Positive Pressure Ventilation
PRIS	Propofol Infusion Syndrome
RA	Right Atrium
RCA	Right Coronary Artery
RV	Right Ventricle
RVEF	Right Ventricular Ejection Fraction
SA	Sinoatrial
SBP	Systolic Blood Pressure
SD	Standard Deviation
SERCA2	Sarco-Endoplasmic Reticulum Calcium ATPase
TnC	Troponin C
TnI	Troponin I
TnT	Troponin T
TOE	Trans-Oesophageal Echocardiography
TTE	Trans-Thoracic Echocardiography
USG	Ultrasonography
VS	Versus

ABSTRACT

TITLE:

"COMPARISON OF EFFECTS OF GENERAL ANAESTHESIA INDUCTION WITH THIOPENTONE-FENTANYL AND PROPOFOL-FENTANYL COMBINATIONS ON LEFT VENTRICULAR SYSTOLIC FUNCTION ASSESSED BY TRANS-THORACIC ECHOCARDIOGRAPHY: A ONE YEAR RANDOMISED CLINICAL TRIAL"

Background:

Assessing the effect of induction agents on systolic function of the heart may help us in selecting the appropriate induction agents in patients who are at risk of developing intraoperative cardiac dysfunction.

Objectives:

To assess the effects of Thiopentone-Fentanyl vs. Propofol-Fentanyl on left ventricular systolic function in patients undergoing non-cardiac surgeries under general anaesthesia using trans-thoracic echocardiography

Methods:

Sixty volunteers aged between 18-60 years belonging to ASA grades I and II were studied. Echocardiography was performed before and after induction of general anaesthesia and measurements (LVEDD, LVESD, LV fractional shortening and LV ejection fraction) were tabulated for all the volunteers. Statistical analysis was performed using appropriate tests.

Results:

LVFS decreased from 39.37% ± 9.52 to 27.47% ± 8.46 for Propofol-Fentanyl group against 38.97% ± 8.60 to 37.97% ± 7.39 for Thiopentone-Fentanyl group before and after GA induction respectively (p-value < 0.0001). LVEF reduced from 70.90% ± 10.27 to 53.30% ± 14.21 in Propofol-Fentanyl group whereas in the Thiopentone-Fentanyl group LVEF before and after GA induction was 70.67% ± 10.04 and 69.83% ± 9.52 respectively (p-value <0.0001)

Conclusion:

General anaesthesia induction with Propofol-Fentanyl produces significant myocardial depression as compared to Thiopentone-Fentanyl and should therefore, be used cautiously in patients at risk of myocardial depression.

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INTRODUCTION

Post induction hypotension is a known complication in patients undergoing general anaesthesia[8,30]. This may be induced due to peripheral vasodilation, decreased systemic vascular resistance, direct myocardial depression and decreased systolic function of the heart etc[5,8].

Thiopentone and Propofol are two of the most widely used induction agents for general anaesthesia. Fentanyl is an opioid which has been extensively used as an intra-operative analgesic agent. All the aforementioned drugs are known to affect the haemodynamic parameters in patients with pre-existing diseases as well as those without[3].

Most of the studies that have aimed to assess haemodynamic effects of the above drugs have employed measures like NIBP, ECG, advanced cardiac output monitors and trans-oesophageal echocardiography. Conventional non-invasive methods like NIBP and ECG provide a very limited assessment. Advanced CO monitors involve specialised equipment and reagents. Trans-Oesophageal echocardiography, while a very good tool in expert hands, is an invasive procedure not without its share of complications[30]. Trans-Thoracic Echocardiography (TTE) on the other hand, is completely non-invasive, reproducible (despite being operator dependent) and provides a very accurate assessment of cardiac function including but not limited to Left Ventricular Ejection Fraction (LVEF), Left Ventricular end-diastolic volume (LVeDV), left ventricular end-diastolic pressure (LVeDP) etc. It is a potent tool for assessing the systolic function of the left ventricle. In recent years, its application has begun to include assessment of bedside haemodynamic parameters

especially in ICUs and emergency rooms[1]. While in the ICUs, conventional 2-D Trans-Thoracic Echocardiography has gained acceptance, it has found limited application in the operating room with Trans-Oesophageal route mainly being used especially in patients undergoing cardiac surgeries[30].

While both Thiopentone and Propofol have been studied extensively as standalone agents, their respective combinations, especially with fentanyl, have not been studied thoroughly in patients undergoing non-cardiac surgeries under GA.

We aim to study the effects of thiopentone-fentanyl and propofol-fentanyl combinations as induction agents in general anaesthesia on the cardiac function in a non-invasive manner with the help of trans-thoracic echocardiography in the operating room by assessing LV dimensions and diameter during systole and diastole hence calculating the LVEF and fractional shortening.

OBJECTIVE

TO ASSESS THE EFFECTS OF THIOPENTONE-FENTANYL VS. PROPOFOL-FENTANYL ON LEFT VENTRICULAR SYSTOLIC FUNCTION IN PATIENTS UNDERGOING NON-CARDIAC SURGERIES UNDER GENERAL ANAESTHESIA USING TRANS-THORACIC ECHOCARDIOGRAPHY

REVIEW OF LITERATURE

Many studies have reported a reduction in arterial blood pressure after injection of intravenous anaesthetic agents propofol and thiopentone.

One of the major criticisms of propofol is the greater degree of reduction in arterial BP after GA induction as compared to thiopentone. The primary mechanism appears to be reduced systemic vascular resistance and a mild negative inotropic effect. However, direct CVS effects and their mechanisms are a matter of controversy[17-22].

In a study conducted in 1993 by Aun, Sung, O'Meara, Short and Oh showed a greater degree of CVS depression on IV induction of GA in children with propofol as compared to an equipotent dose of thiopentone[16].

Glenski, Friesen, Hassnein and Henry in 1988 concluded that Fentanyl, Sufentanyl and Isoflurane did not significantly affect cardiac function (as assessed with echocardiography) in children undergoing cardio-vascular surgery[2].

Gauss, Heinrich and Walder-Smith conducted a study in 1991 in Germany comparing etomidate, propofol and thiopentone with the help of trans-oesophageal echocardiography. They found propofol to cause both negative inotropic effects and afterload reduction while thiopentone showed only the former[3].

Chraemmer-Jørgensen, Høilund-Carlsen, Marving and Christensen studied the effects of elective or rapid sequence induction on left ventricular ejection fraction. They concluded that sudden cardiovascular impairment occurs during laryngoscopy and intubation in both elective and rapid sequence induction. This may produce a higher burden on an already poorly perfused heart[23].

Danish team of Nielsen, Ahlburg, Schnedler and Christensen compared effects of thiopentone and propofol in young and elderly patients. They found that propofol produced a greater degree of decrease in MAP in both age groups[26].

In 1991, Mulier, Wouters, Van Aken, Vermaut and Vendermeersch studied the effects of both propofol and thiopentone with transoesophageal echocardiography. They concluded that the cardio-depressant effects of propofol were more pronounced than thiopentone when either drug was given as a single bolus dose. They also confirmed that the effects of propofol on systemic arterial pressure were caused due to its negative inotropic effects[14].

Studies at University of Natal, Durban, South Africa regarding possibility of early intubation with higher doses of thiopentone and associated haemodynamic changes found that even at higher doses, patients induced with thiopentone remained haemodynamically stable. On the other hand, use of propofol, while producing equivalent intubating conditions, was associated with marked hypotension.[24-25]

In Gumma, Japan in 2003, using reduced doses of propofol and thiopentone, 1mg/Kg and 2 mg/Kg respectively, Kadoi, Saito, Ide, Toda, Sekimoto, Seki et al observed that lesser haemodynamic changes were observed with Propofol than with Thiopentone. They also observed a greater decrease in MAP in the Propofol group[15].

Sørensen, Dolven and Rasmussen in a study conducted in Denmark in 2011 found that Thiopentone had a faster onset of action and lead to lesser fall in both HR and BP in elderly patients as compared to Propofol when both were administered along with alfentanil[4].

Uygur et al in 2014 compared propofol, etomidate and thiopentone all in combination with fentanyl for induction concluding that fentanyl-etomidate combination was safest among the three in terms of haemodynamic stability while propofol-fentanyl combination affected haemodynamic parameters the most. In this study, cardiac output was measured with impedance cardiograph[5].

Dahlgren, Settergren, Ribeiro and Brodin studied changes in left ventricular diameter during IV induction of anaesthesia. Using 2-D transthoracic echocardiography, they found that measurements were in agreement with earlier studies conducted using radionuclide or thermodilution methods.[27]

In 2015, Berli et al used 2D echo for assessment of LV systolic function in goats undergoing GA concluding the 2D echo is a valid, non-invasive method to assess LV systolic function in awake and anaesthetised goats[6].

Kratz et al in 2016 concluded that focussed Trans-Thoracic Echocardiography by anaesthesiologists can provide new information that may alter the haemodynamic management of unstable high-risk noncardiac surgery patients in the operating room[7].

In 2019, Magunia et al used Trans-Thoracic Echocardiography for assessment of Right Ventricular Function as affected by GA induction and PPV. They found that while RVEF and RV stroke volume were preserved even after induction of GA and PPV, there was significant reduction in baso-apical right ventricular function[8].

Another study in 2019 where Dalla et al used Trans-Thoracic Echocardiography to assess the effects of GA + PPV on RV and LV, observed reduction of both LV and RV function systolic function to levels indicating dysfunction in patients undergoing GA with propofol along with PPV[9].

In 2019, Hino et al compared Thiopentone and Propofol in combination with remifentanil concluding that Thiopentone in this combination produces lesser reduction in mean arterial pressure as compared with propofol. Thus, Thiopentone is a better induction agent for general anaesthesia for avoiding hypotension in middle aged or elderly patients[10].

In 2006, Stein, Tiwari, Thomas, Hunt, Levent, Stoddard et al studied the effect of anaesthesia on LV structure and function in rats using trans-thoracic echocardiography. They found that using even higher doses of thiopentone (up to 35 mg/Kg) in rats lead to only minimal depression in cardiac function[28].

While extensive studies on animal models are available including those on hamsters[11], mice[12], swine[13] and others, despite extensive search, no studies were found which compared thiopentone-fentanyl with propofol-fentanyl as induction agents for GA based on Transthoracic Echocardiographic assessment of LV systolic function in humans. Hence, we aim to assess the effects of thiopentone-fentanyl vs. propofol-fentanyl on left ventricular systolic function in patients undergoing non-cardiac surgeries under general anaesthesia using trans-thoracic echocardiography.

BASIC SCIENCES

ANATOMY[29, 32, 36,]

The heart is a trapezoidal muscular organ situated in the middle mediastinum along with the pericardium and roots of great blood vessels. It is encased in the pericardium which is a fibro-serous membrane covering the heart and roots of its great blood vessels – ascending aorta, pulmonary trunk and superior vena cava. Functionally, the heart is a double, self-adjusting suction and pressure pump which helps to drive blood via pressure gradients by the means of vessels to and from the whole body. It consists of four chambers the right and left atria and the right and left ventricles. The atria are receiving chambers which then pump the received blood into the ventricles which are the discharging chambers. The duality of the pump is owing to the fact that the right and left sides of the heart perform synchronous but independent functions which come together to become more than the sum of their parts.

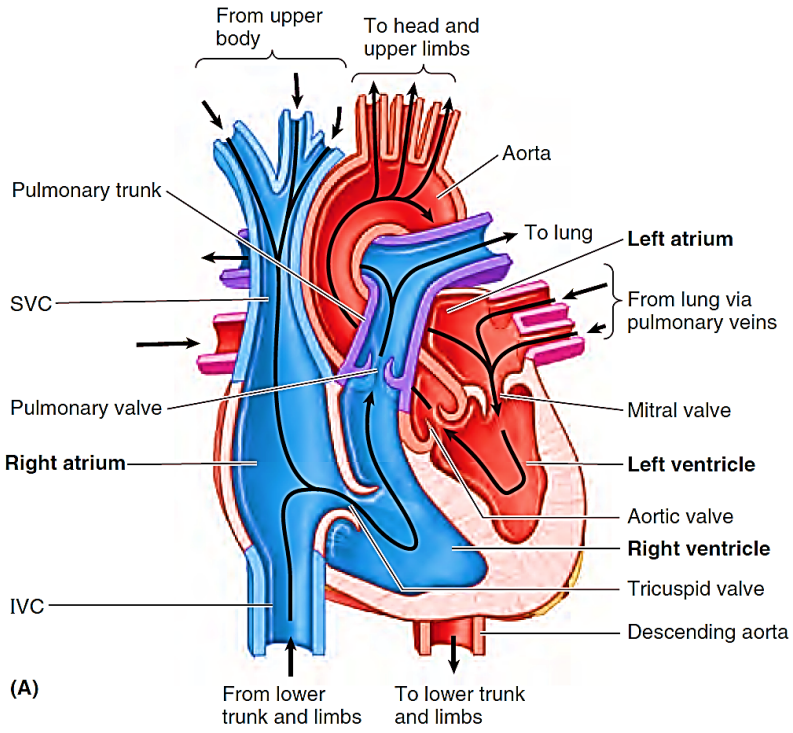


FIGURE 1: Anatomy of the Heart

The heart is composed of three layers. From superficial to deep these are

EPICARDIUM

- Thin external layer (mesothelium) – formed by visceral layer of pericardium
- Protects the heart

MYOCARDIUM

- Thick, helical muscular layer in middle
- Controls pumping of heart
- Differential thickness on right and left sides
    - Due to different pressure and resistance
    - Left side is thicker as it has to pump blood through the whole body

ENDOCARDIUM

- Thin internal layer – endothelium and sub-endothelial connective tissue
- Covers lining of blood vessels and valves
- Helps modulate cardiac function
- Contains Purkinje fibres – help in synchronising ventricular contractions
- Acts as *blood-heart barrier* – controls myocardial extracellular environment

Due to the thickness of myocardium and barrier function of the endocardium, heart needs its own blood supply in the form of *coronary circulation* which arises from the right and left coronary sinuses just distal to the aortic valve.

The circulation through heart can be schematically divided into three parts which work at different pressure levels while sharing the same flow. First, the *pulmonary circulation* which is a low-resistance/low-pressure system on the right side of the heart. The right atrium receives deoxygenated blood from the body through the superior and inferior venae cava and pours it into the right ventricle which then pumps it through the pulmonary artery to the lungs. The tricuspid valve between the right atrium and ventricle, and the pulmonary valve between the right ventricle and pulmonary artery prevent the backflow of blood respectively into the previous chamber. The left atrium receives the oxygenated blood from lungs through pulmonary veins, pours it into the left ventricle which eventually propels it through the aorta into the systemic circulation. This *systemic circulation* is the second part of circulation through the heart which is a *high-resistance/high-pressure system*. Backflow between the left atrium and ventricle and the left ventricle and aorta is prevented by the mitral and aortic valves respectively.

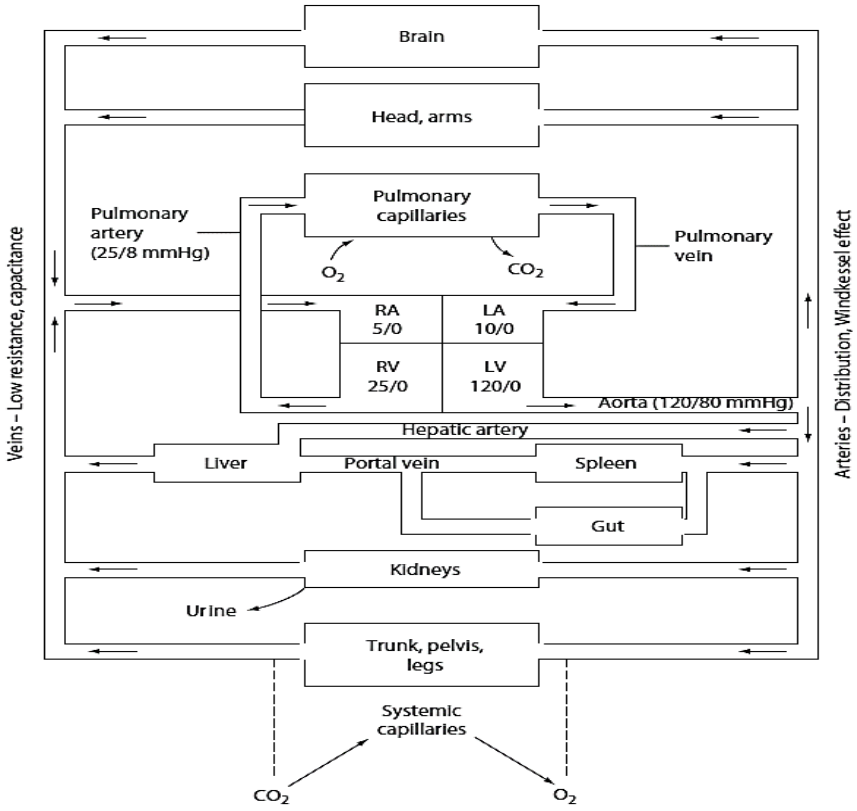


FIGURE 2: Schematic of Blood Flow in Body

Separation between the pulmonary and systemic circuits is maintained with the help of the interatrial septum superiorly and the interventricular septum inferiorly

Inter-Atrial Septum

- Septum primum – Mesenchymal connective tissue
- Septum secundum – Muscle

Inter-Ventricular Septum

- Muscular
- Septum membranaceum – small fibrous part

The third part of this circulation is the blood supply to the heart itself – the coronary circulation. Its main constituents are the Left Anterior Descending (LAD) artery, Left Circumflex (LCx) artery and the Right Coronary Artery (RCA) along with their accompanying veins. Blood flow to the heart muscles occurs during diastole when there is a positive pressure gradient in these vessels owing to the aortic blood pressure being higher than the left ventricular pressure.

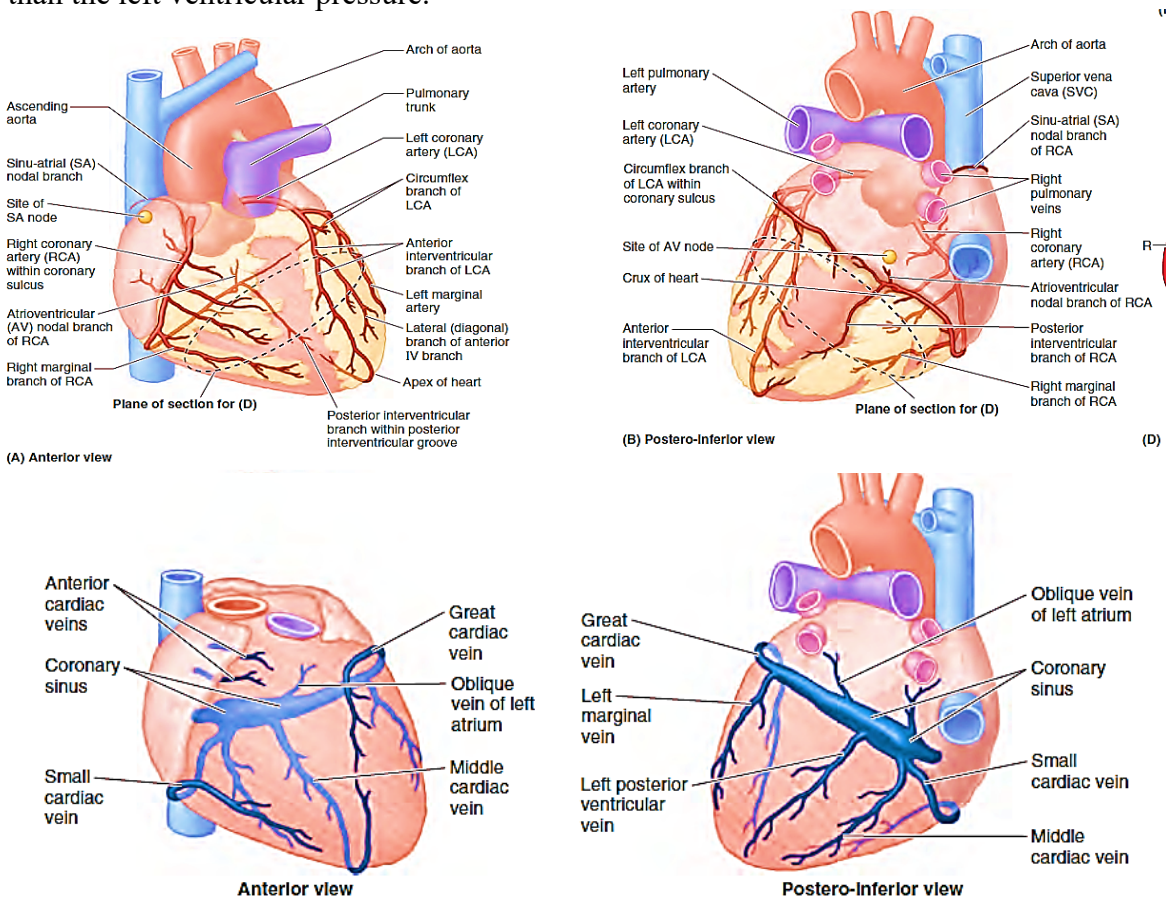


FIGURE 3: Blood Supply of Heart

Surface anatomy of the Heart

The borders of the heart are variable and depend on the position of the diaphragm and the build and physical condition of the person.

- The superior border corresponds to a line connecting the inferior border of the 2nd left costal cartilage to the superior border of the 3rd right costal cartilage.
- The right border corresponds to a line drawn from the 3rd right costal cartilage to the 6th right costal cartilage; this border is slightly convex to the right.
- The inferior border corresponds to a line drawn from the inferior end of the right border to a point in the 5th intercostal space close to the left MCL; the left end of this line corresponds to the location of the apex of the heart and the apex beat.
- The left border corresponds to a line connecting the left ends of the lines representing the superior and inferior borders.

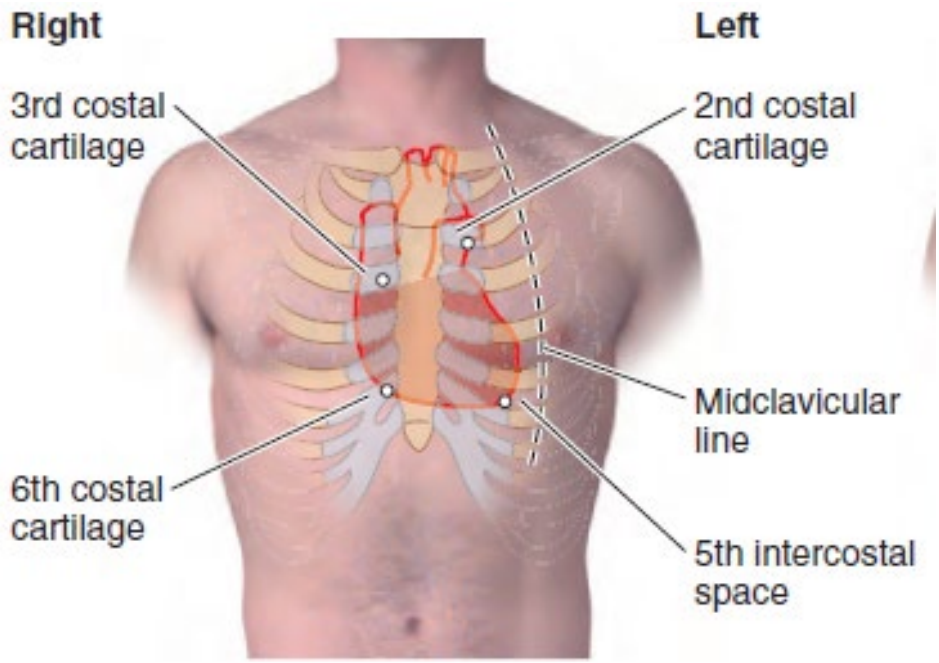


FIGURE 4: Surface Anatomy of Heart

PHYSIOLOGY[30-36]

Cellular Anatomy

At the cellular level, the heart consists of three major components: cardiac muscle tissue (contracting cardiomyocytes), conduction tissue (conducting cells), and extracellular connective tissue. The cardiomyocytes together with the surrounding connective tissue, make up a *myofibre* many of which in turn are connected to each other with collagen strands. The extracellular matrix is produced from fibroblasts which produce components responsible for the mechanical and functional properties of the heart. These include

- Collagen – stiffness of myocardium
- Elastin – elastic properties of myocardium
- Glycoproteins
- Matrix Metalloproteinases – breakdown of collagen and extracellular proteins

Fifty percent of cardiomyocyte volume is made up of myofibrils; the remainder consists of mitochondria, nucleus, sarcoplasmic reticulum, and cytosol.

The cardiac muscle is striated like a skeletal muscle and contains actin and myosin filaments similarly. The muscle fibres are arranged in series and parallel with one another with cell membranes visible as *intercalated discs* fusing with one another forming *gap junctions* which allow for rapid diffusion of ions helping in propagation of impulses. Thus, cardiac muscle is a *syncytium* of many heart muscle cells in which the cardiac cells are so interconnected that when one cell becomes excited, the action potential rapidly spreads to all of them. Division into two functional syncytia the *atrial syncytium* and *ventricular syncytium* allows the atria to contract a short time ahead of ventricular contraction, which is important for effectiveness of heart pumping.

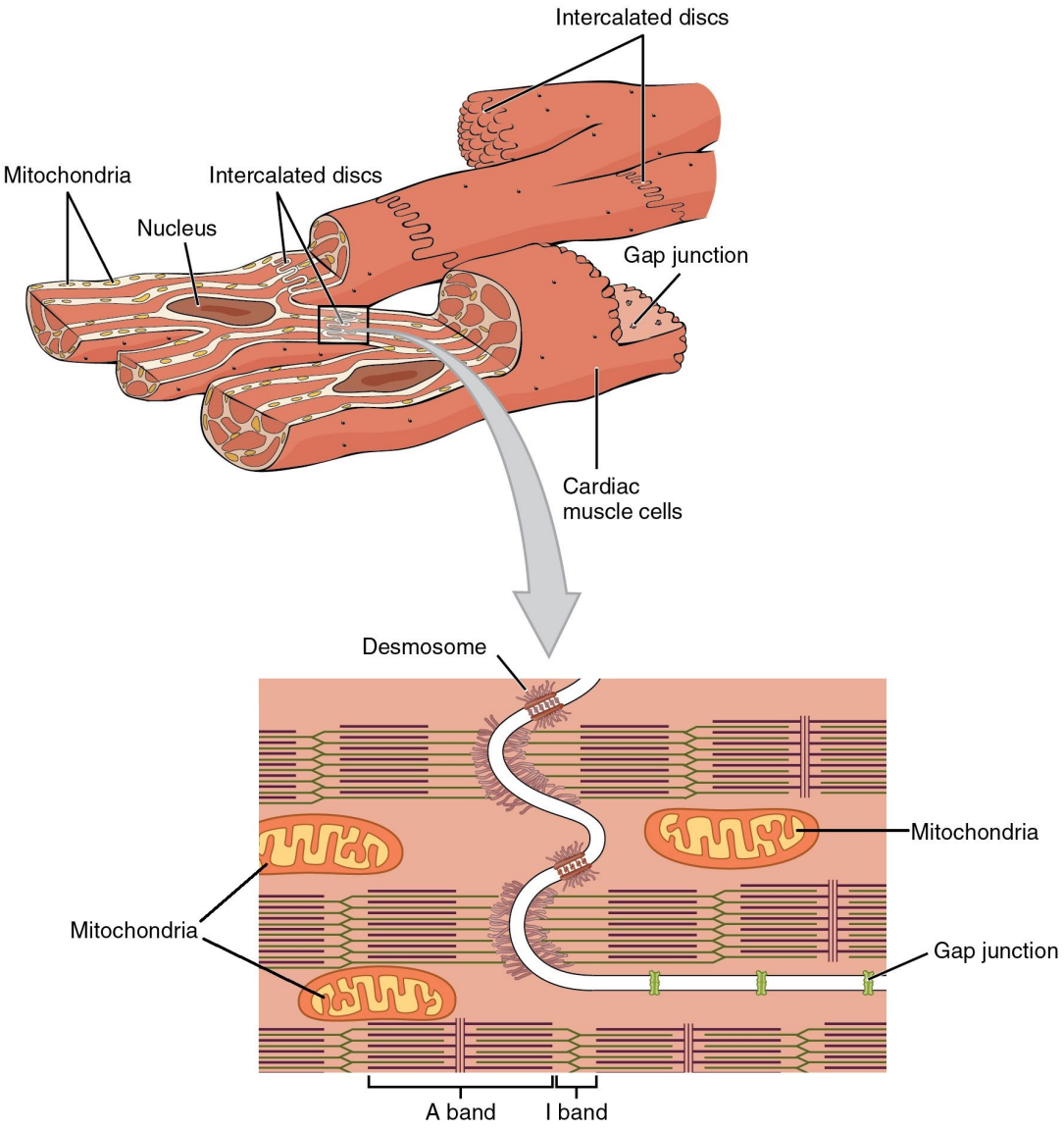


FIGURE 5: Cellular anatomy of Cardiac Muscle

Normally, potentials are not conducted from the atrial syncytium into the ventricular syncytium directly through this fibrous tissue. Instead, they are conducted only by way of a specialized conductive system

Electrical Conducting System of the Heart

Electrical activation of the heart plays a crucial role in its mechanical performance. It consists of specialised *nodal tissue* which initiates the heartbeat and co-ordinates the contractions of all the four chambers. Highly specialised conducting fibres then conduct the generated impulses to different areas of the heart. Thereafter, the striated cardiac muscles propagate the impulses helping all the areas to contract in a synchronised manner.

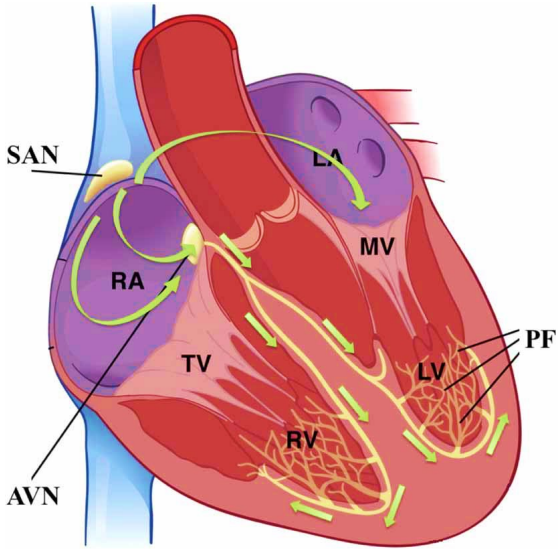


FIGURE 6: Conduction System of Heart

The sinoatrial (SA) node is the primary cardiac pacemaker by virtue of having the highest firing rate. If there is a decrease in its firing rate or marked delays in conduction, secondary pacemakers take over the function. In decreasing order of firing rate, these are atrioventricular (AV) node, bundle of His followed by the Purkinje system and then the ventricular muscles.

After depolarisation of the SA node, the anterior, middle (*tract of Wenckebach*), and posterior (*tract of Thorel*) internodal pathways transmit the impulse rapidly through the RA myocardium to the AV node. A branch of the anterior internodal pathway (i.e., *Bachmann*

bundle) also transmits the SA node depolarization from the RA to the LA across the atrial septum.

This electrical conduction is closely related to the electrocardiogram as shown in the figure below

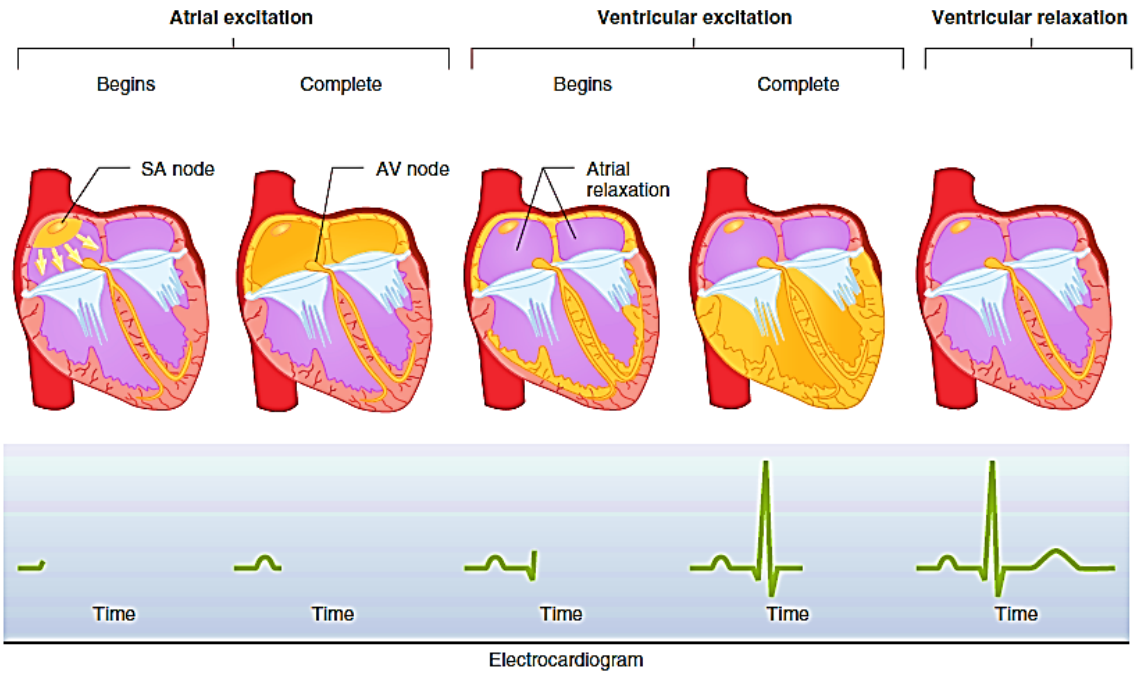


FIGURE 7: Conduction Correlation with ECG

Cardiac muscle contraction

The cardiomyocytes can be divided into three functional components:

- Excitation system
- Contractile system
- Excitation-Contraction Coupling (ECC)

Excitation System

Specialised conducting cardiomyocytes (*Purkinje Cells*) propagate the action potential to individual cells. This eventually leads to contraction of the myocyte though the sarcolemmal system. The action potential itself results from depolarisation of the cell membrane. Depolarisation and repolarisation of the cardiac myocytes result from ion fluxes across the plasma membranes mediated by voltage gated ion channels for sodium (Na+), potassium (K+), Calcium (Ca2+), and chloride (Cl−).

Two types of action potentials are observed in the heart

1) *Fast Response Action Potential*: His-Purkinje System
   Atrial and ventricular cardiomyocytes
2) *Slow Response Action Potential*: Pacemaker cells in SA node and AV node

The resting membrane potential of -90mV is maintained with the help of electrochemical gradient of K+ across the cell membrane.

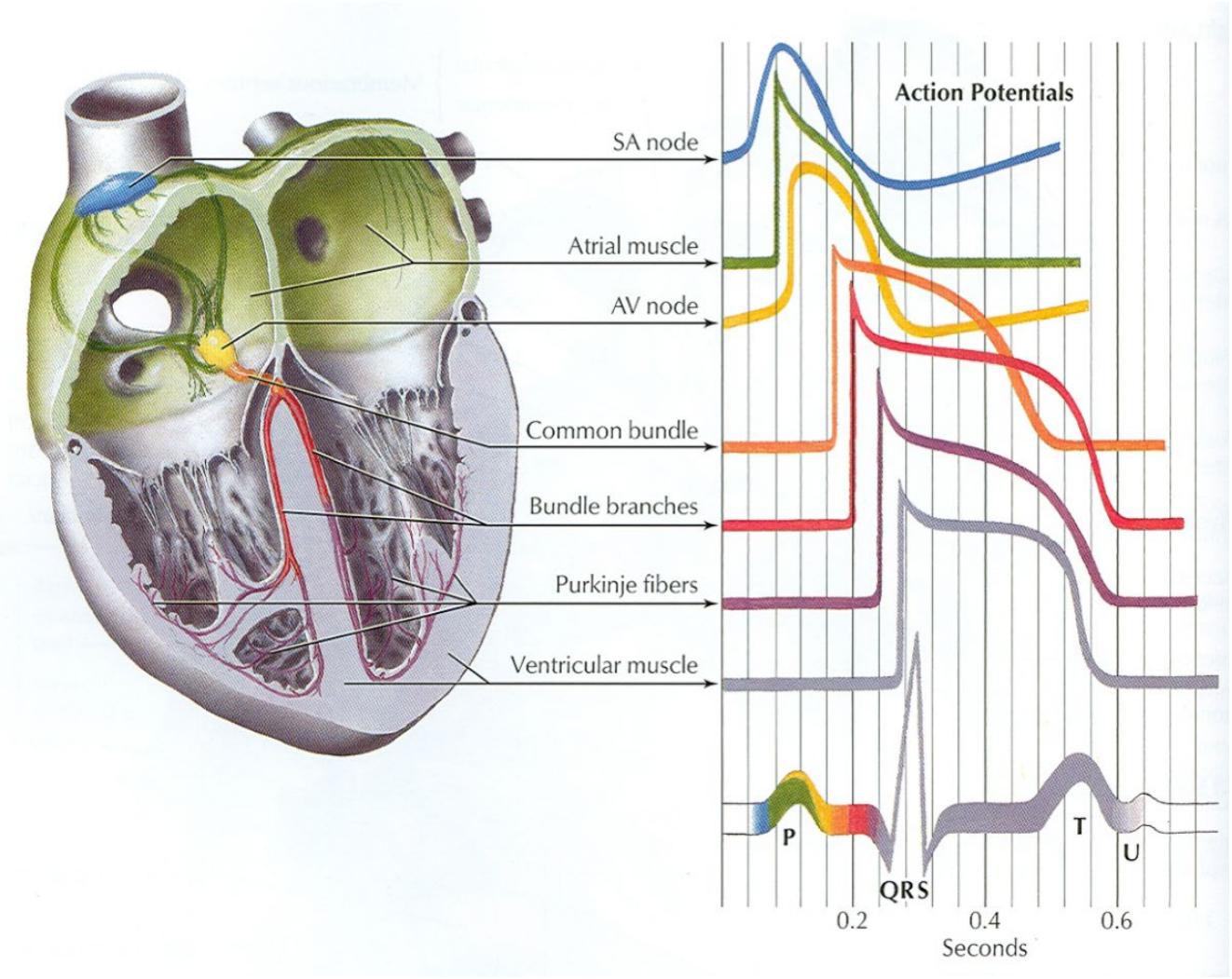


FIGURE 8: Action Potentials of Different Parts of Conduction System

In cells where fast response action potential is seen, rapid influx of Na+ initiates the action potential leading to an extremely rapid upstroke (*phase 0*) and overshoot. This depolarisation is propagated when the membrane potential reaches a critical threshold level. The rapid upstroke is followed by a brief period of limited repolarisation (*phase 1*) caused mainly by activation of a transient outward K^+ current (i_{to}). The next phase is the plateau phase (*phase 2*) attributable to influx of Ca^{2+} through the L-type Ca^{2+} channels. This is balanced by the efflux of K+ through several channels causing the inward rectifier current (i_k), delayed rectifier current (i_{k1}) and the transient outward current (i_{to}). When the efflux of potassium through the three outward currents exceeds the influx of calcium, repolarisation (*phase 3*) occurs. This returns the membrane potential to its resting state with a transmembrane potential of -90mV. The next phase (*phase 4*) where very little ionic flux is observed is part of the diastole. The Na+ influx-K+ efflux in this phase is maintained by the Na+-K+ ATPase.

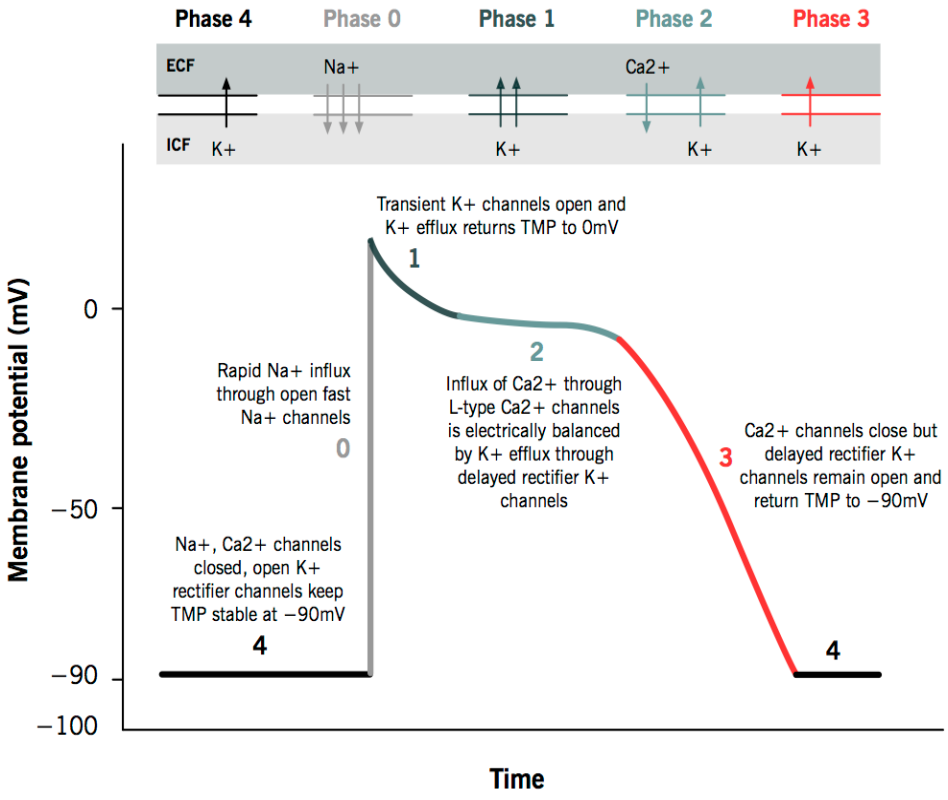


FIGURE 9: The Cardiac Action Potential

In the pacemaker cells, which show slow-response action potential, there is a capability of spontaneous diastolic depolarisation during phase 4 and thus, generation of automatic cardiac rhythm. The pacemaker potential is somewhat unstable and starts at about -60mV. A total of three inward and two outward currents contribute to the spontaneous pacemaker activity in these cells. The three inward currents include i_{CaL} and i_{CaT} which are Ca^{2+} currents through L-type and T-type channels respectively along with the mixed cation current I_f. The inward rectifier current (i_k) and delayed rectifier current (i_{k1}) constitute the outward currents in this phase. In the slow response action potentials, the phase 0 is much less steep, phase 1 is absent and phase 2 and 3 are indistinguishable from each other.

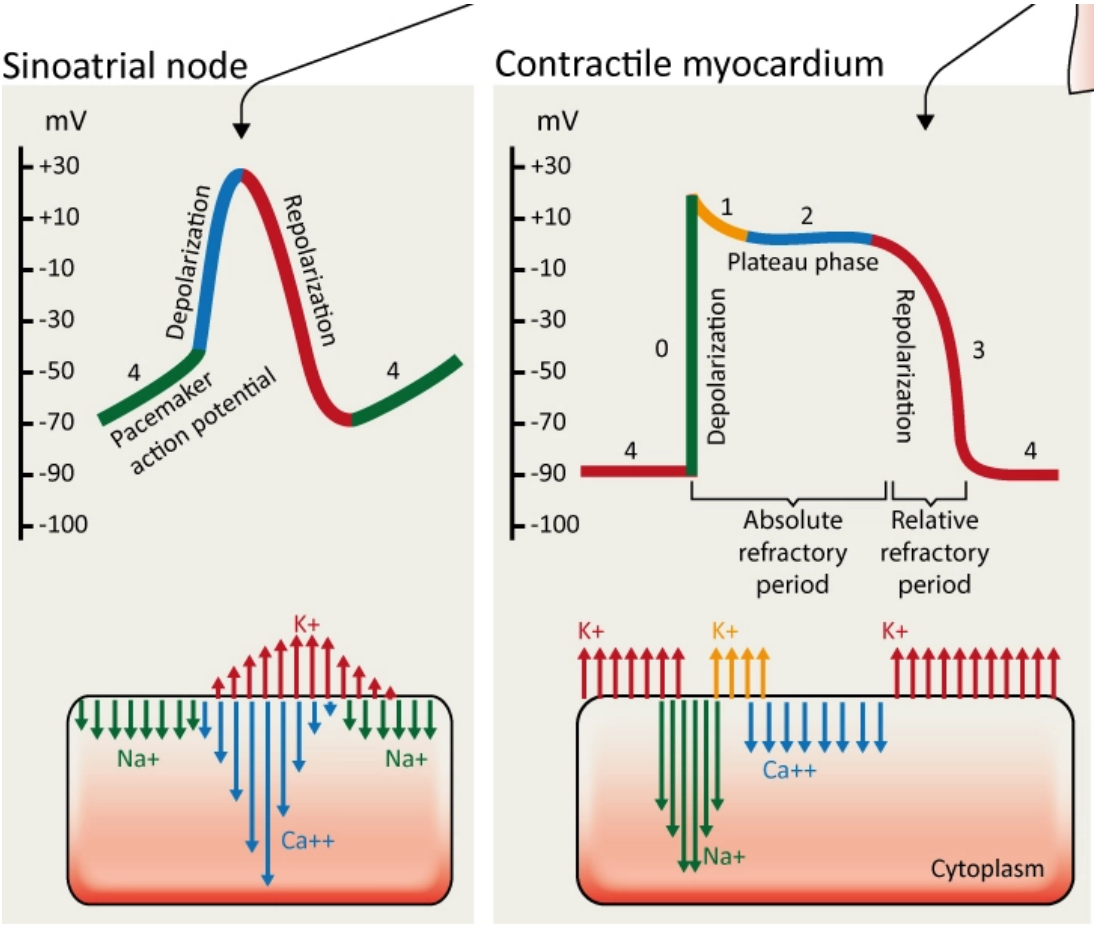


FIGURE 10: Action Potentials of Different Parts of Myocardium

Refractory Periods

Refractory periods during contraction of cardiac muscles allow for complete emptying of the ventricles before the next cycle of contractions can set in. These are governed by the number of sodium channels ready for activation. Three types of refractory periods are seen

- *Absolute Refractory Period:* No depolarisation allowed
- *Effective Refractory Period:* Non-propagated depolarisations may occur
- *Relative Refractory Period:* Stimuli stronger than normal can cause a full depolarisation

Apart from the above three, there is also a hyperexcitable *supranormal period* where even weak stimuli can cause action potentials

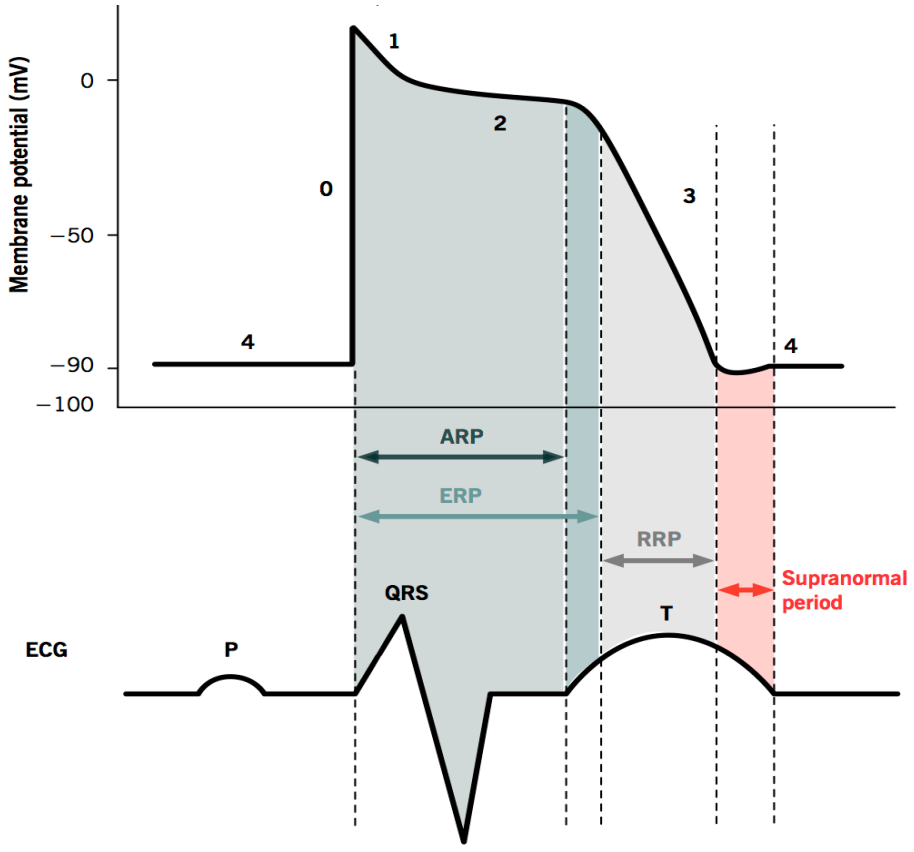


FIGURE 8: Refractory Periods in Cardiac Action Potential

Contractile System

- Contractile Proteins:
  - Actin: Thin filament. Contains two helical chains
  - Myosin: Thick filament. Made up of 300 myosin molecules each containing two functional domains, body or filament and bilobar myosin head. The head in turn consists of one heavy and two light chains. The heavy head chain has two further domains one larger and one smaller. Larger one interacts with actin at actin cleft and has an ATP-binding pocket where myosin ATPase is located. The smaller domain is flexible and is attached to the two lighter chains
- Regulatory Proteins:
  - Tropomyosin: double stranded α-helix. Winds around actin and acts as its backbone
  - Troponin heterotrimer complex
    - Troponin C (TnC): Ca2+ receptor
    - Troponin I (TnI): Inhibitor of actin-myosin interaction
    - Troponin T (TnT): Links troponin complex to tropomyosin
- Cytoskeletal Proteins: provide the organization of microenvironments within the cell for enzyme and protein activity and interaction.
  - Microfilaments
  - Microtubules: a major role in intracellular transport and cell division
  - Intermediate filaments: important in normal mitochondrial function and behaviour. The *desmin* intermediate filament in cardiomyocytes connects the nucleus to the plasma membrane and is important in the transmission of the stress and strain of contractile force between cells.

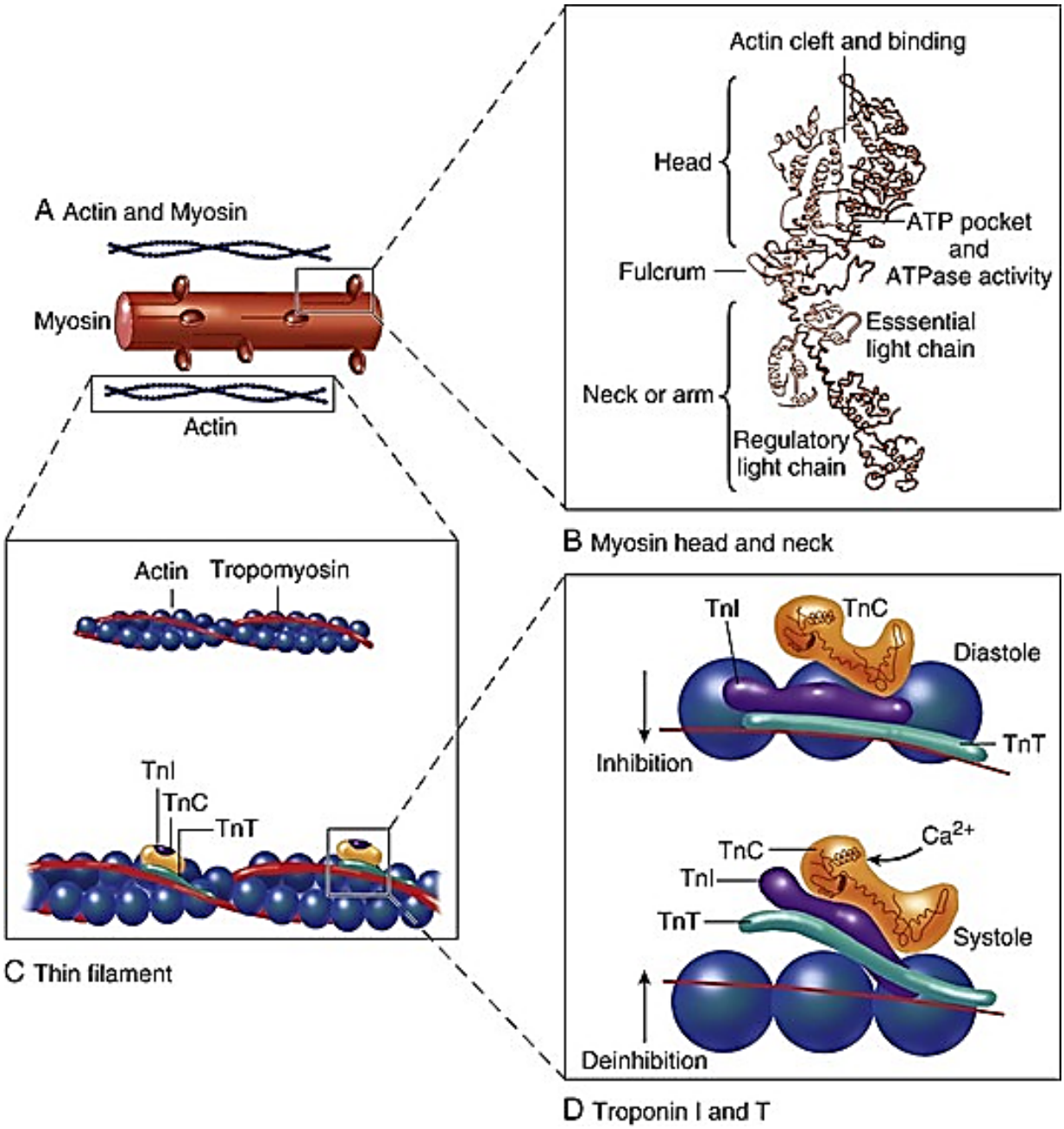


FIGURE 12: Contractile System of Cardiac Muscle

All the above come together to form the basic working unit of the contractile system i.e., *sarcomere.*

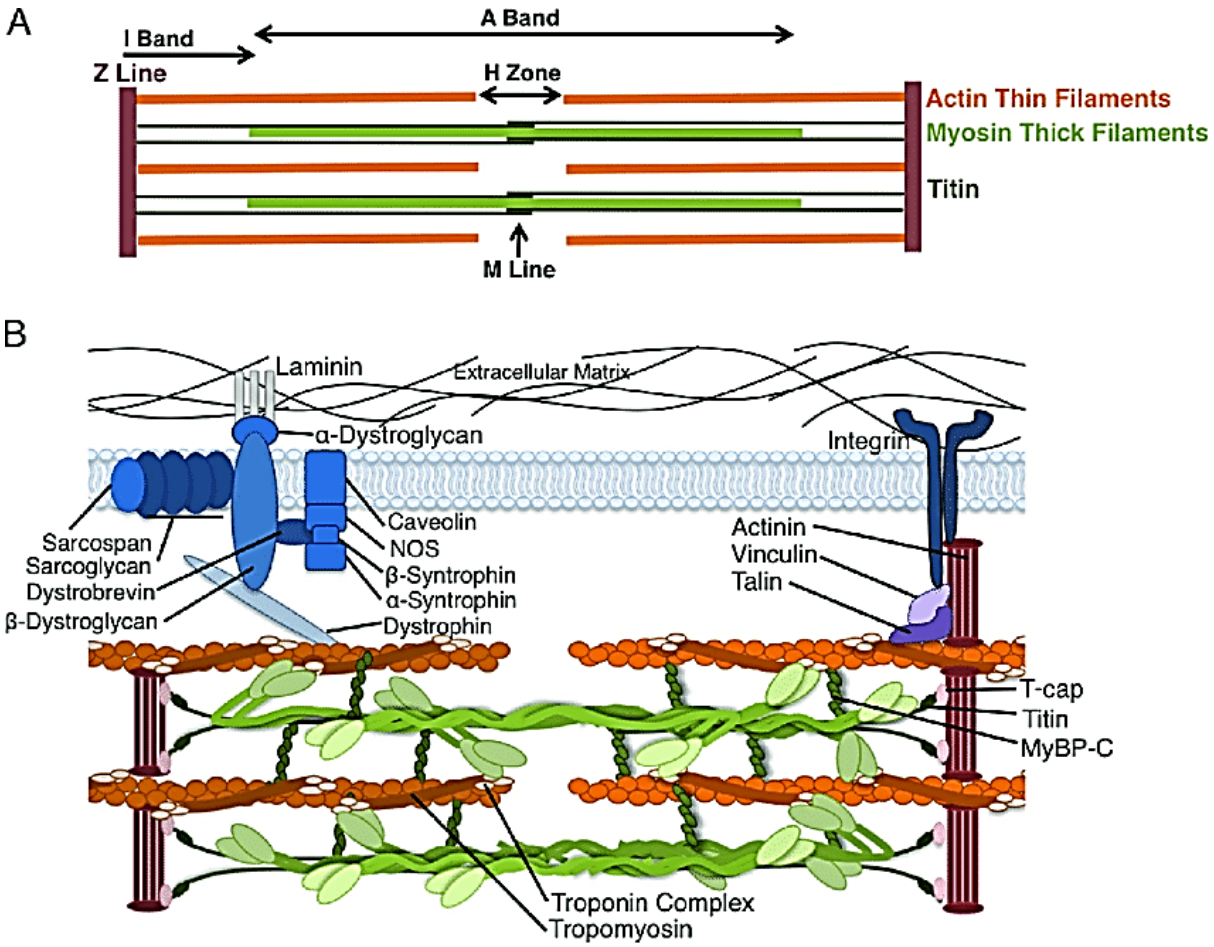


FIGURE 13: Sarcomere

Sarcomeres are attached to each other in series by the *Z lines* [from German *Zuckung* meaning contraction] where thin actin filaments are anchored which form transient sliding interactions with thick myosin filaments. The *M line* (myosin only), *I band* (actin only), and *A band* (overlapping actin-myosin) are anatomical features defined by their components and appearance in polarized light. The Z line and the M line are connected to each other by *Titin* which is the principal determinant of the passive properties of the myocardium at small ventricular volumes. It also contributes to the elastic properties and force production of the sarcomere through its extensible region in the I Band. Coordinated shortening of the sarcomere creates contraction of the cardiomyocyte.

Excitation-Contraction Coupling

An action potential is generated in the SA node which travels to the myocytes activating the L-type, voltage gated calcium channels. This causes influx of calcium (the ubiquitous second messenger) into the myocyte. This calcium in turn causes release of calcium from the sarcoplasmic reticulum through ryanodine receptors. Due to this *calcium induced calcium release* there is a rise in the intracellular calcium concentration. This calcium then interacts with the troponin-tropomyosin system eventually leading to actin-myosin interactions thus resulting in contraction of the cardiac muscles. The influx of calcium into the cells is regulated by Na^{+}/Ca^{2+} exchange (NCX) channels working together with the Na/K ATPase channels both located on the myocyte membrane. The NCX helps in efflux of excess calcium in exchange for sodium, a process requiring considerable energy against an electrochemical gradient. The excess sodium thus accumulated is removed by the Na/K ATPase.

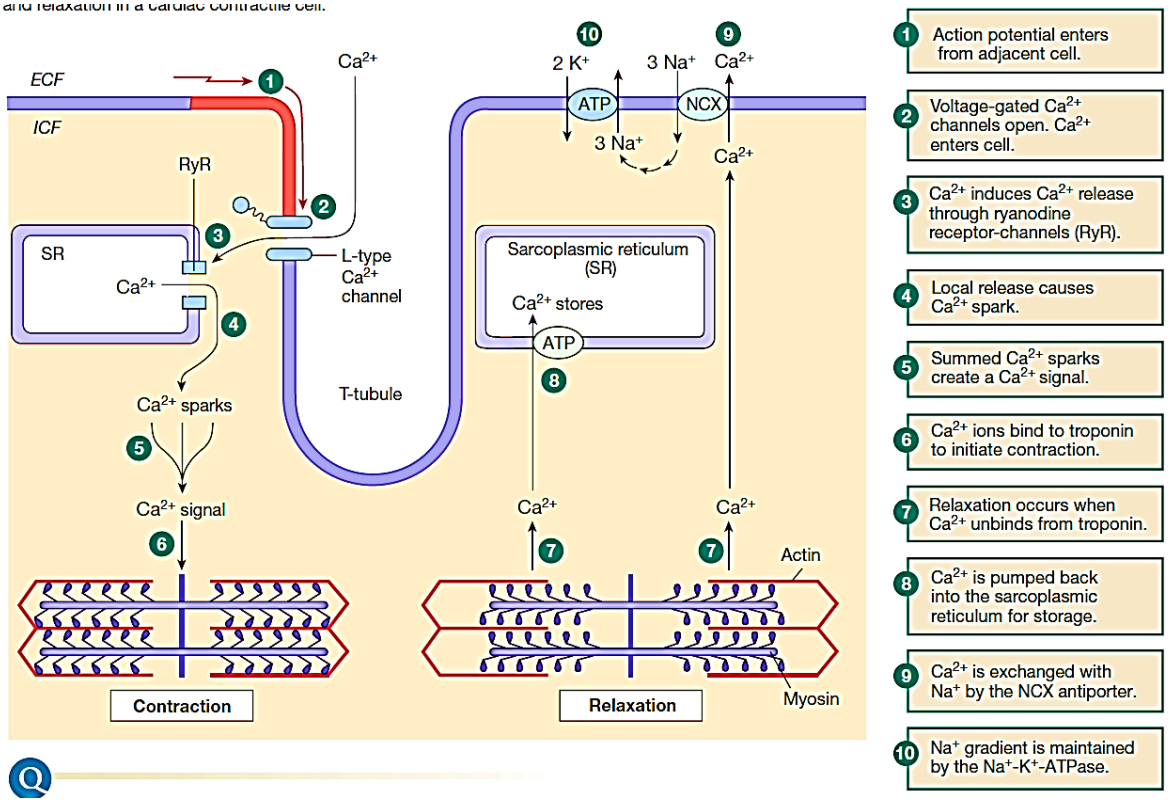


FIGURE 14: Excitation-Contraction Coupling in Cardiac Muscle

The excitation-contraction coupling forms the biochemical-biomechanical basis for cardiac function.

Contractility and Inotropy

These are the most commonly used and arguably abused terms for evaluation of cardiac function. Although these are used interchangeably, both of these refer to specific properties of the cardiac muscles and thus, the cardiac function. *Contractility or contractile state* is the inherent capacity of the myocyte or cardiac muscle to shorten in the absence of *load*, whereas *inotropy or inotropic state* is used in the context of phosphorylation state and Ca^{2+} handling/dynamics.

For instance, a positive inotropic response would refer to an increase in shortening of the sarcomere owing to increased availability and sensitivity of Ca^{2+} at the myofilaments. This increased availability and sensitivity is itself caused by phosphorylation of the L-type Ca^{2+} channel, phospholamban, and troponin-I by beta receptor agonists such as norepinephrine. This positive inotropic response will be translated into increase force of contraction of the cardiac muscle, hence translated into a positive contractile response.

Load – Preload and Afterload

The term *load* refers to the external forces or constraints affecting the lengths of the sarcomeres. The relationship between sarcomere length and the maximum force that can be developed is a central issue with respect to contraction of ventricular myocardium. Studies have demonstrated that a curvilinear relationship exists between sarcomere lengths and the force of contraction of cardiac muscles. There exists a range of lengths where the relationship is almost linear i.e., with increasing length of sarcomere, the force of contraction increases. Below these levels, the contractile force is inadequate and above these lengths, there is plateau rendering it ineffective. the length that causes

the maximal force development is termed maximal length: L_{max}. This signifies that when resting tension of the muscle reaches near maximal, there is no net gain in muscle performance. These forces acting on the cardiac muscles prior to beginning of the contraction are referred to, collectively, as *preload*.

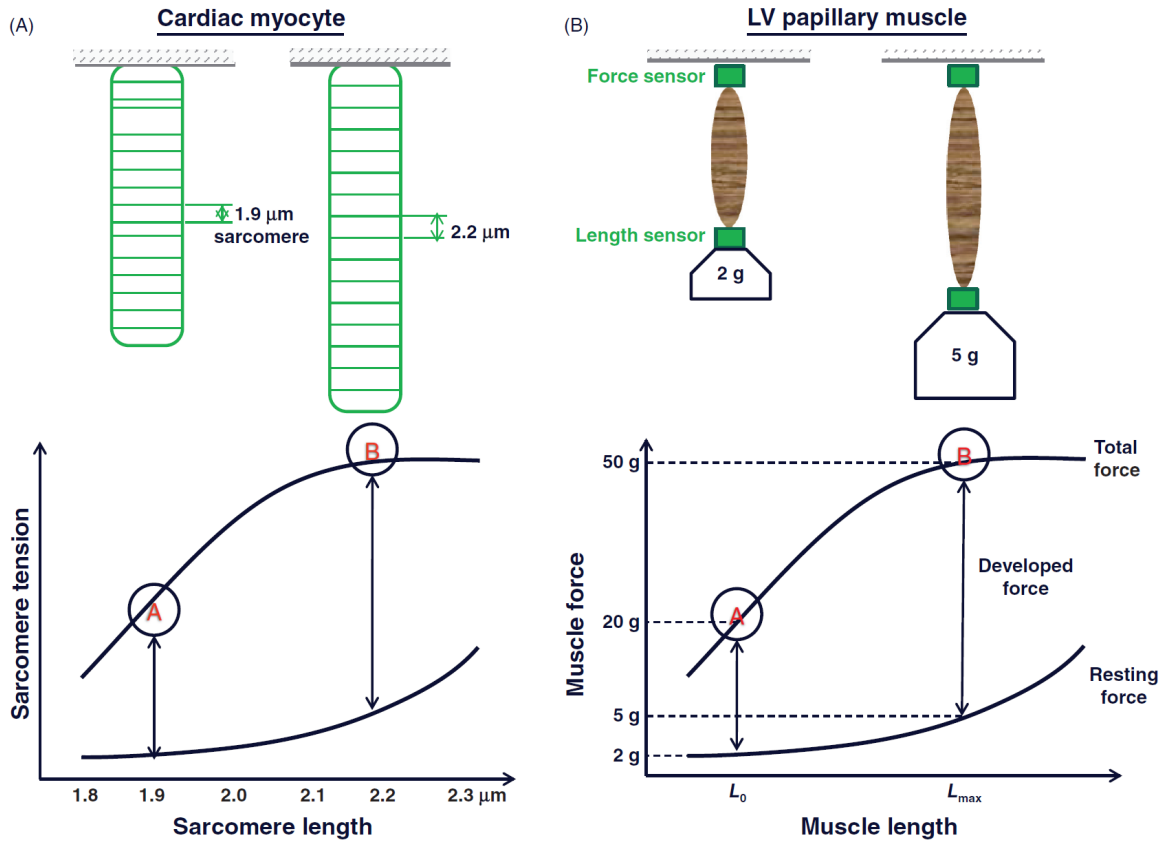
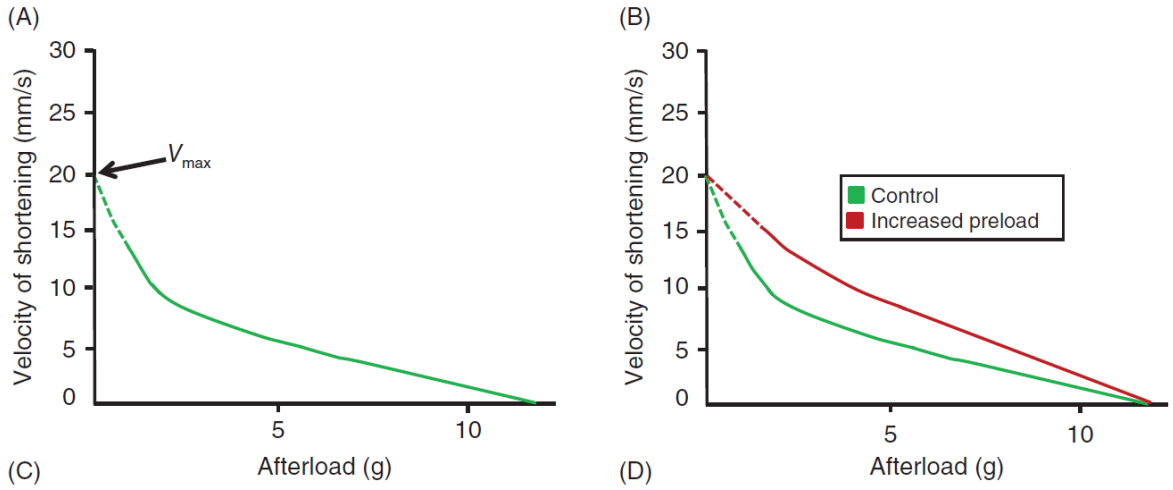


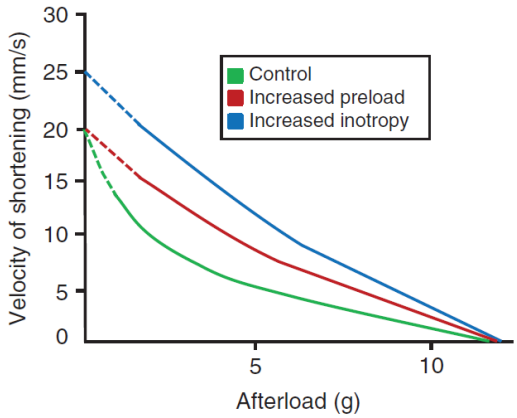
FIGURE 15: Cardiac Muscle and Load

The additional resistive force that is placed upon the muscle once it begins to shorten, such as during an isotonic contraction, is defined as *afterload*. There is an inverse relationship between the velocity of muscle shortening to the amount of resistive force or afterload placed upon the muscle. Studies have demonstrated that there is a significant fall in velocity of shortening at high afterloads, whereas at very low afterloads, the velocity of shortening approaches a near linear relationship. The theoretical value at which muscle is shortening in the absence of any afterload is termed V_{max}.



GRAPH 1A: Effect of load on Velocity of Shortening of Cardiac Muscle

At any given afterload, increased preload will yield a higher velocity of muscle shortening. This is because the resting sarcomere length has been increased and hence an improved mechanical advantage for cross-bridge formation at the onset of contraction. The increase in preload, however, does not change the intrinsic contractile state of the cardiac muscle itself as evidenced by no change in V_{max}. Exposure to positive inotropic agents such as norepinephrine enhances the intrinsic contractile state of the cardiac muscles thus leading to an increase in V_{max}. while both interventions will increase velocity of shortening at a given afterload, only an increase in inotropy will cause an increase in V_{max}.



GRAPH 1B: Effect of load on Velocity of Shortening of Cardiac Muscle

These relationships demonstrate the important interactions of load and contractile state upon muscle shortening performance and therefore are important to consider in the evaluation of cardiac function.

CARDIAC FUNCTION

Cardiac function or cardiac pump function is the process by which blood is ejected from the LV in a pulsatile fashion. During this process, there are continuous changes in the geometry, motion and intrinsic function of the cardiac muscle itself. The first step in overall evaluation of cardiac function is thus, examination of changes in the LV pressure and volumes during specific phases – the systole and diastole.

Cardiac Cycle

The electrical and mechanical events taking place during a single heartbeat are known as the *cardiac cycle*. In general, the main determinants of the mechanical events, affecting the atria and ventricles, are the electrical events. The electrical events of the cardiac cycle are closely represented by the electrocardiogram (ECG) while the mechanical events may be understood better through the pressure-volume curve.

Electrical Events in Cardiac Cycle

The initiation of a heartbeat with the generation of an impulse at the SA node is the starting point for the electrical events of the cardiac cycle. The SA node, by virtue of being able to generate impulses at the highest frequency among the conduction tissue of the heart is the natural pacemaker. These events are represented by the ECG which is a tracing of the potential differences generated by the heart recorded at the surface of the body.

Impulse generation at SA node and its subsequent spread via specialised conduction tissue that leads to atrial contraction is represented by the *P wave* of the ECG. The impulse reaches the AV node at the junction of interatrial and interventricular septa. Owing to the slow

conduction at AV node, there is a slight delay in conduction represented by the *PR interval* on the ECG. The depolarisation then propagates through the Bundle of His, right and left bundle branches and subsequently to Purkinje fibres. This spread is represented by the *QRS complex* on the ECG. Thereafter repolarisation of the ventricles takes place represented by the *T wave* on the ECG.

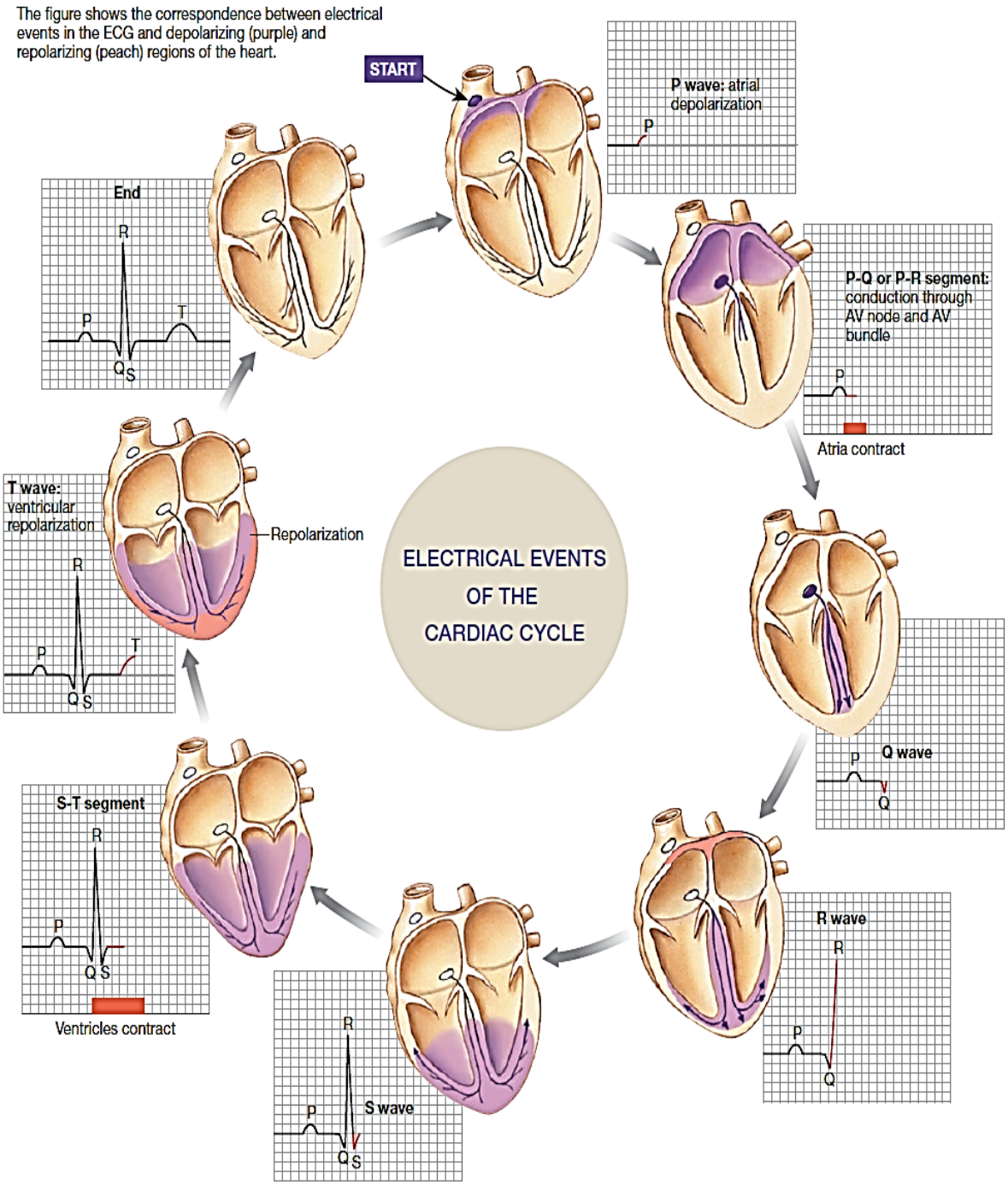


FIGURE 16: Electrical Events of Cardiac Cycle

Mechanical Events in Cardiac Cycle

The purpose of contraction of heart is to pump blood through the body. We must remember that blood flows from high pressure to low pressure and that contraction increases pressure while relaxation decreases pressure. Classically, the cardiac cycle is divided into diastole and systole, when the ventricles get filled with blood from the atria and when the ventricles eject the blood into the aorta and pulmonary artery respectively.

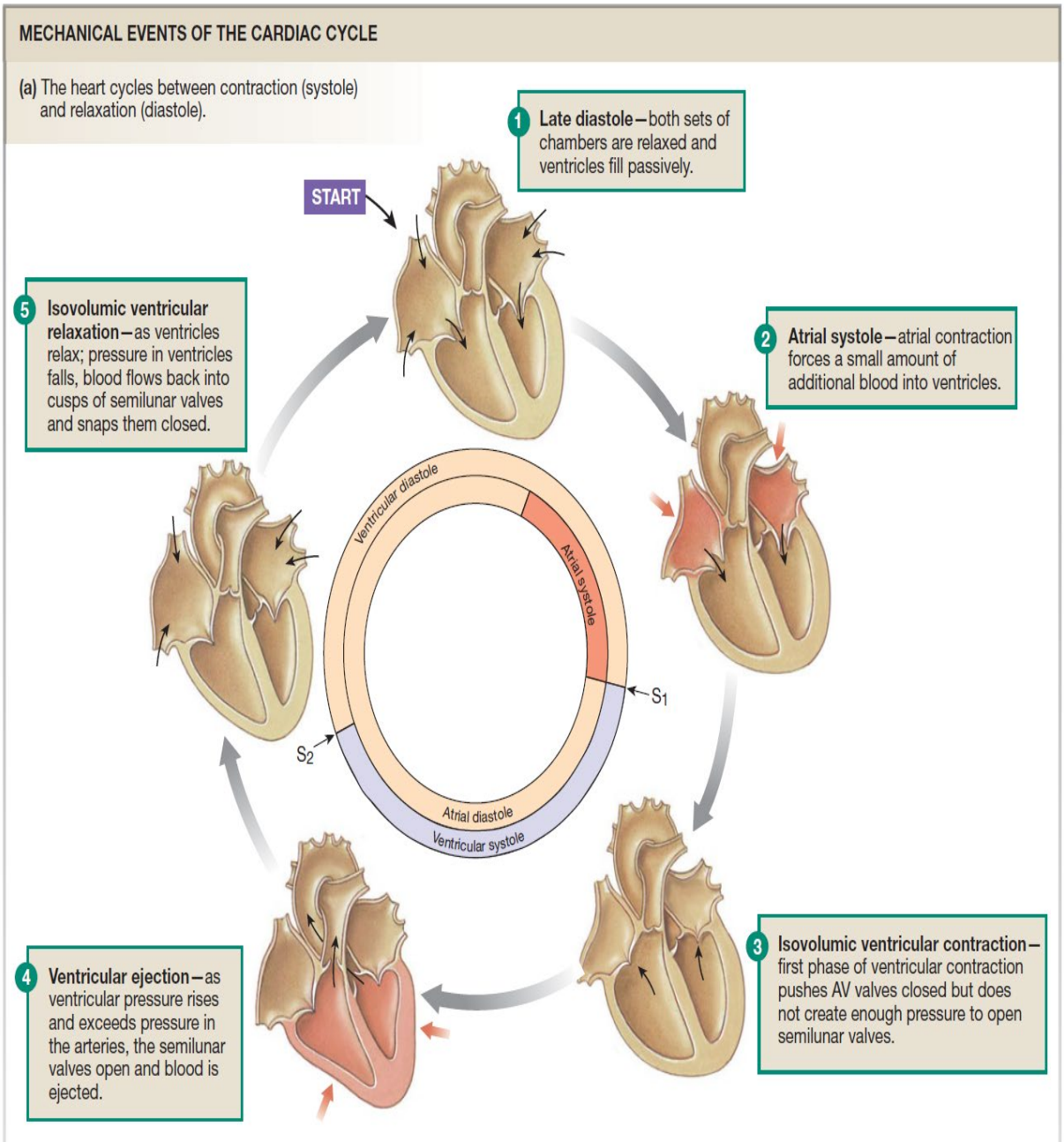


FIGURE 17: Mechanical Events of Cardiac Cycle

The pressure-volume loop is a graphical representation of the relationship between intraventricular pressure and ventricular volumes during one cardiac cycle.

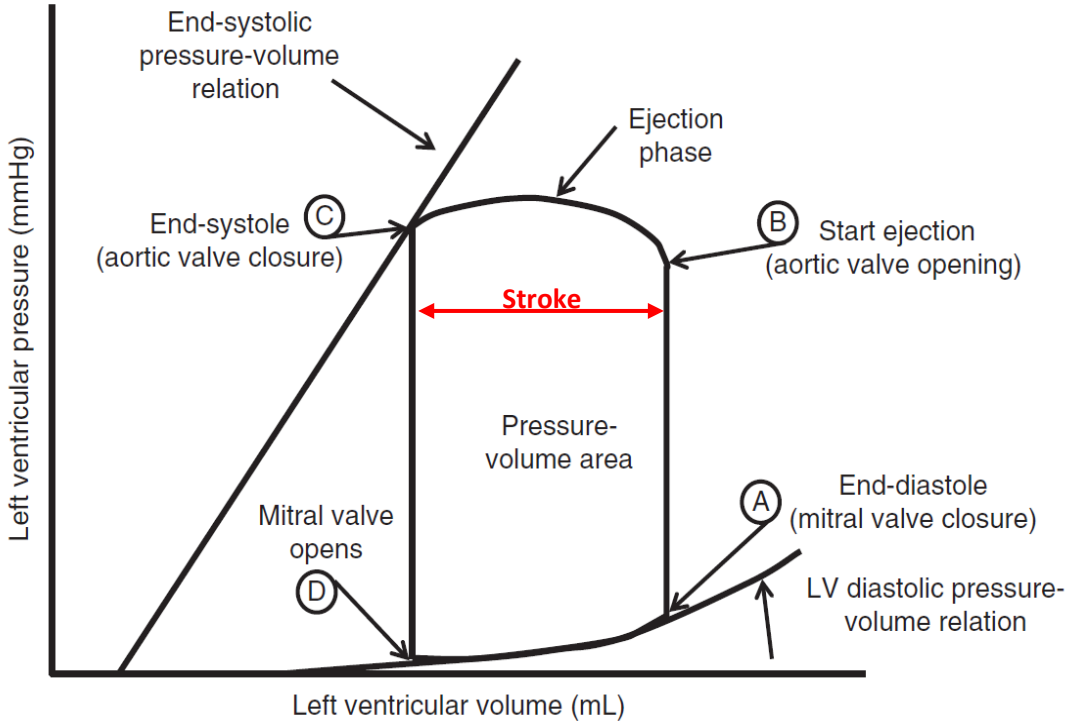


FIGURE 18: Pressure-Volume Loop

The first stage of cardiac cycle consists of diastolic filling of the left ventricle just after opening of the AV valves. Initially the diastolic filling is passive relying on the recoil of the ventricles (rapid LV filling phase) while active filling takes place later with the atrial systole. During this stage, the intraventricular volume rises significantly while the intraventricular pressure is raised only slightly. The pulmonary venous return continues and thus, the atrial pressures increase prior to the opening of the AV valves. These atrial pressure changes give rise to the *v wave* of the atrial and jugular venous pressure tracing. Also, the LV pressures fall during the early passive filling phase of this stage as LV relaxation occurs faster than filling. The end of this rapid filling phase coincides with a rise in LV diastolic pressure which is reflected back into the atrium owing to the open mitral valve. Atrial volumes and pressures rise as pulmonary venous return continues. As the atrial volumes approach maximum, electrical depolarisation of the atria occurs marked by the *P* wave of the ECG and *c wave* on the atrial pressure trace. Atrial contraction occurs which forces blood through the AV valves into

the ventricles adding to the LV end-diastolic volume. This phenomenon is also known as the *"atrial kick"*. The volume of blood required for this to occur is dependent upon the duration of the previous diastole and strength of atrial contraction. With slower heart rates, the major filling occurs by relaxation of the LV while at faster heart rates, the time for passive filling is shortened and majority of LV filling is due to the atrial contraction. The end of this stage is marked by the closure of the AV valves which occurs as a result of change in the atrio-ventricular pressure gradient and contraction of the ventricles. The reversal of this pressure gradient causes AV valve leaflets to float upwards which are then shut by the raised tension in papillary muscles caused due to ventricular contraction. This closure causes local turbulence and can be heard on auscultation as the first heart sound or *S1*. The completion of atrial contraction and closure of the AV valves marks the end of diastole and is represented by the beginning of the *R wave* on the ECG. The end of this stage also heralds the beginning of the next stage of isovolumetric contraction.

The second stage is transient where the ventricular contraction begins with the atrioventricular, aortic and the pulmonary valves closed. While the intraventricular volume remains the same, the pressure rises rapidly. Thus, this stage is known as that of *isovolumetric contraction*. This causes the AV valves to bulge slightly into the atria giving rise to the *c wave* on atrial pressure trace. During this stage, the ventricular shape resembles a sphere due to the increase in circumference and decrease in apex to base dimensions. It represents the maximal period of myocardial fibre shortening and the contractile energy at this stage causes a rapid increase in the intracavitary pressure to the level of the aortic diastolic pressure. As the intraventricular pressure reaches the systolic arterial pressure (aortic for LV and pulmonary arterial for RV) the semilunar valves open and the third stage of ejection begins. The maximum rate of pressure development at this stage, the peak $+dP/dt$ is measured during this stage as one of the indices of heart function assessment. Acute changes in this parameter can reflect changes in the inotropic state of the heart. However, as inotropic states are highly influenced by vasoactive drugs, vasomotor tone and load (particularly LV afterload) it is quite challenging to interpret these values as representative of changes in underlying inotropy and contractility of the heart. These changes in ventricular geometry have been referred to as a *"twist"* and are an important

mechanism for efficient ventricular force generation. The peak of the *R wave* on the ECG represents the end of diastole and depolarisation of the cardiac muscle entering into the isovolumetric contraction phase.

The third stage is *systole* and the ejection of blood from the ventricles. During this stage the ventricular volume decreases while the intraventricular pressure increases until it equalises with the arterial pressure leading to closure of the semilunar valves. With opening of the aortic valve, the left ventricle shortens and shifts from an isometric form to on isotonic form. The ejected blood quickly reaches maximum velocity and constitutes the stroke volume. This ejected volume is not immediately transported to the peripheral blood vessels owing to inertial and resistance factors. It gets accommodated in the aorta by stretching of its elastic wall and increasing its volume. This imparts potential energy to the aorta which is used to maintain the aortic pressures during aortic valve closure and diastole. This is also how a forward flow of blood is maintained irrespective of the phase of cardiac cycle. As this stage nears its end, the ventricular pressures peak and begin to fall. Momentarily, the aortic and ventricular pressures equilibrate followed by a reversal which causes blood to attempt to regurgitate into the ventricles. This backflow pushes on the semilunar valves and causes their closure. This rapid deceleration and closure of the valves produces the *incisura* or *dicrotic notch* on the aortic pressure trace and is utilised to synchronise the end of systole with the second heart sound *S2* which itself is caused due to the turbulence caused by closure of the semilunar valves. During this phase, many volumetric indices for assessment of cardiac function can be measured as the pressure traces, specifically the dicrotic notch, affords us the ability to synchronise the cardiac cycle. The LV volume during the isovolumetric phase, just prior to opening of AV valves is the LV end-diastolic volume while the LV volume at the dicrotic notch is the LV send-systolic volume. The difference between these two is the stroke volume. These volumes are highly sensitive to loading conditions and intrinsic contractile state of the heart apart from the duration of cardiac cycle.

The fourth and final stage is that of *isovolumetric relaxation* when the intraventricular pressure decreases rapidly while the ventricular volume remains the same until ventricular pressure reaches

the atrial pressure and AV valve opens again and the next cardiac cycle begins. This is a highly energy dependent period of cardiac cycle as significant amounts of ATP is utilised for Ca^{2+} movement into the sarcoplasmic reticulum and across the sarcolemma. This is a phase of active relaxation of the ventricles affected by phosphorylation state, inotropic state and also directly affected by load. The preload and afterload significantly affect the rate of isovolumetric relaxation and the rate of ventricular pressure decrease ($-dP/dt$) during this phase is also one of the significant cardiac function indices. The slope of the plot of log of LV pressure decline with time yields the time constant for active relaxation τ *(tau)*. This reflects the relative efficiency and function of active relaxation. Under equivalent or prespecified loading conditions, τ can help in evaluating defects in Ca^{2+} re-sequestration thus helping in detecting SR dysfunction.

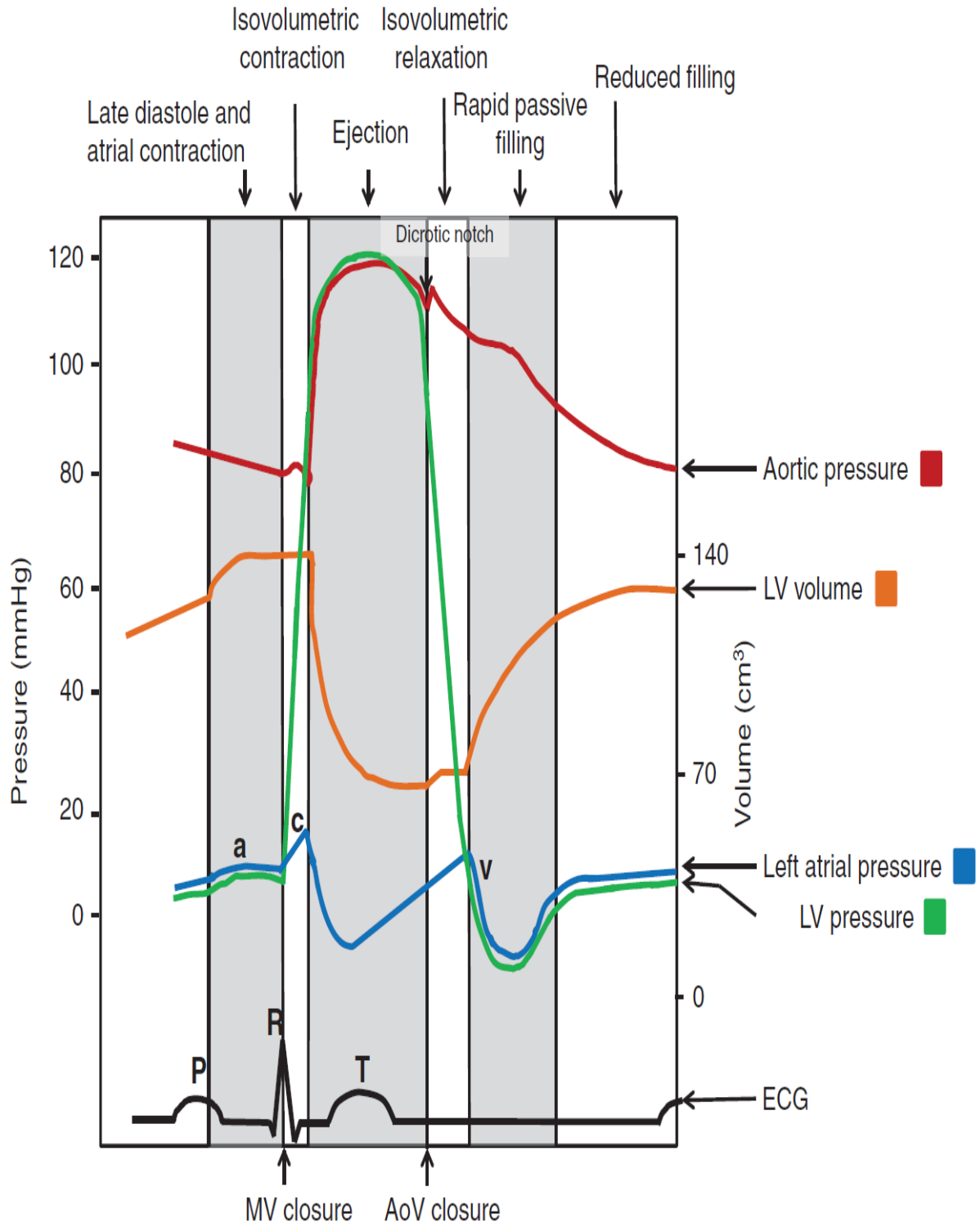


FIGURE 19: WIGGER'S DIAGRAM

The events of the cardiac cycle can be plotted together in the form of the *Wigger's Diagram.*

Left Ventricular Pump Function and its Assessment

The basic and arguably dependent variable of LV pump function assessment is *stroke volume*. It is the difference between the LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV). The external physical work done during the ejection phase of the cardiac cycle is known as the *stroke work*. It is a fundamental determinant of myocardial ATP utilisation and oxygen consumption. Mathematically, it can be approximated as the product of stroke volume and mean arterial pressure. It is affected by afterload, preload or both and thus, the LV load-ejection relationships can provide important insights into underlying myocardial performance and contractility.

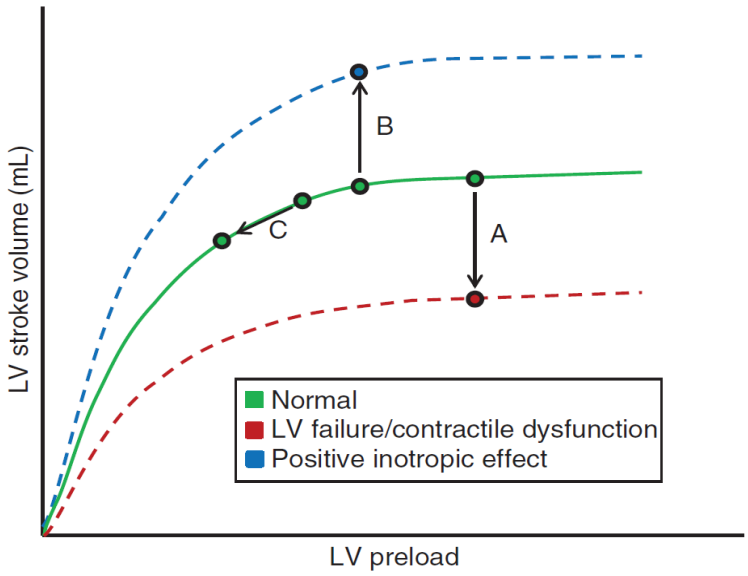
Stroke volume can be measured with various invasive and non-invasive methods with the basic aim of measuring the volume of blood pumped by LV across the aortic valve. The current gold standard for LV volumetric measurements is cardiac magnetic resonance imaging (cMRI). The most commonly employed non-invasive method is transthoracic echocardiography which determines stroke volume through Doppler measurements of flow across valves. The invasive methods include thermodilution, dye dilution, radionuclide imaging or electromagnetic flow probes. These methods are used to measure various indices used for evaluation of cardiac function as listed in the following tables. The principals involved for their application to evaluate of cardiac function are described later.

TABLE 1: Methods for Measuring Specific Indices of Cardiac Function

		Key parameters	**Key advantages**	**Key disadvantages**
Invasive	*Thermodilution catheter*	Cardiac output, RV/PA pressure	Accuracy	Flow averaged No direct measure of LV volumes
	Conductance catheter	LV pressure/volumes	Simultaneous LV pressure and volumetric estimates	Positioning and analysis Computations require assumptions
	Cine-ventriculography	LV pressure/volumes	Accuracy of LV pressure and volume	Prolonged/repeated measures problematic Requires contrast agent
Non-Invasive	*Radionuclide*	LV ejection fraction/flow perfusion	Direct flow measurements	Radioisotope required LV geometry requires registration with other modality
	Computed tomography	LV geometry/anatomy	High resolution, LV volume and architecture	Requires image reconstruction of acquired slices Gating/sequencing
	Magnetic resonance imaging	LV volume, function, myocardial motion	Accuracy of LV volumes LV Strain mapping	Requires gating and special catheters
	Echocardiography/ ultrasound	LV geometry/ function, Doppler flow	Readily applied, multiple measurements over time	Imaging windows Variability Geometric assumptions

Frank-Starling Relation: relationship between LV pump function and preload

Otto Frank in 1895 and Ernest Starling in 1914 in their seminal works demonstrated that increased atrial pressure achieved by increasing venous return would increase the magnitude of LV ejection. In other words, increased preload would lead to an increase in stroke volume. In recognition of their work, the *Frank-Starling law of the heart* has been named. It can be represented graphically as below.



GRAPH 2: Frank-Starling Law

This brings forth a curvilinear relationship with plateaus at higher preload values similar to ones seen with sarcomere lengths. Therefore, it can be stipulated that under non-pathological conditions, indices of preload measurement like LVEDV, LVEDP, left atrial pressure, pulmonary venous pressure etc. reflect an absolute change in sarcomere length hence acting as a representative of cardiac contractility.

- The downward arrow A indicates a decrease in stroke volume at similar LV preload values. Such downward shift of the curve can be seen in conditions with reduced intrinsic cardiac contractility such as chronic systemic heart failure
- The upward arrow B, showing an upwards shift in the curve is seen in states with increased inotropy usually pharmacological

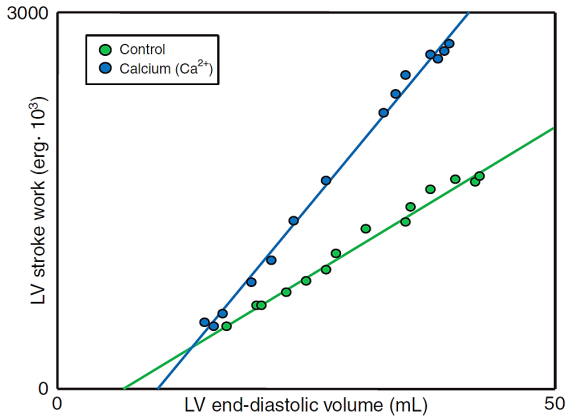
- The third down and leftward arrow C indicates a reduction in LV preload. In such a scenario no change actually occurs in the intrinsic myocardial activity

However, this curve, while quite informative, is not without interpretative considerations which must be factored while assessing LV function

- Small changes in LV preload may lead to large shifts in stroke volume as long as the heart is functioning in the initial rapid ascending limb of the curve while in the later plateau region almost no change is observed even with large increases in preload values
- LV preload range is not equivalent between subjects and thus affects interpretation with its curvilinear shape
- The relationship assumes that LV afterload changes are not occurring, which may be problematic since LV function is affected by afterload as well
- Heart rate can significantly affect LV stroke volume. Faster heart rates will reduce diastolic filling time thus reducing preload while slower heart rates would have the opposite effect

Therefore, the above factors must be taken into account when using preload relationships to assess myocardial contractility.

The indices measured to represent LV preload include end diastolic volume, pressure and segment length. Looking at the stroke work in relation to acute changes in load may help in assessing changes in myocardial contractility. Plotting these on a graph as below with LV preload indices on x-axis and stroke volume on y-axis, a linear relationship is obtained – the *preload recruitable work relation.*



GRAPH 3: Preload Recruitable Work Relation

While revealing intrinsic changes in myocardial contractility, this relationship is also affected by changes in afterload, reflex autonomic responses and is not indexed to pathological conditions. Therefore, it should be interpreted carefully.

Wall Stress: LV pump function and afterload

Studies by Starling in association with Markwalder and Patterson in 1914 were instrumental in demonstrating an inverse relationship between LV stroke volume and increasing arterial pressure or afterload. These studies were, however, performed in isolated preparations of the heart. Owing to the anatomy of heart and arrangement of its muscle fibres aligned in different orientations, there are geometrical constraints to measurement of absolute afterload in an intact heart. To circumvent these, assumptions are made based on *Law of Laplace* and an ellipsoidal geometry.

Law of Laplace states that larger the radius of a vessel, the greater the wall tension required to withstand the pressure exerted by internal fluid. Mathematically it can be represented for spheres as following

$$\Delta P = \frac{2 \cdot T_{sph}}{R}$$

Where T is the surface tension

R is the radius of the sphere and

ΔP is the pressure difference between inside and outside the sphere

Similarly, for cylinders (to measure pressure within a blood vessel) it states

$$\Delta P = \frac{T_{cyl}}{R}$$

Where T is the total of surface tension and elastic wall tension

R is the radius of the cylinder and

ΔP is the pressure difference between inside and outside the cylinder

Using these equations, the product of LV internal radius and pressure are divided by the wall thickness to derive a measure of circumferential wall stress. For the purposes of these calculations, geometrical assumptions are made where the LV short axis just below the papillary muscles is considered symmetrical.

Essentially, this approach puts forth that circumferential wall stress calculations reflect a force per unit cross-sectional area of the ventricular wall and thus, can be considered the resistive force at the onset of contraction. This helps in estimation of the absolute afterload placed upon the LV as the peak circumferential wall stress using LVEDV, LV pressure and wall thickness just prior to aortic valve opening. This is the peak circumferential wall stress at the end of isovolumetric phase of systole and can be considered as the force that must be overcome to enter the ejection phase. The interpretation of LV function-afterload relationship for assessment, as the one with preload, is also dependent on following considerations

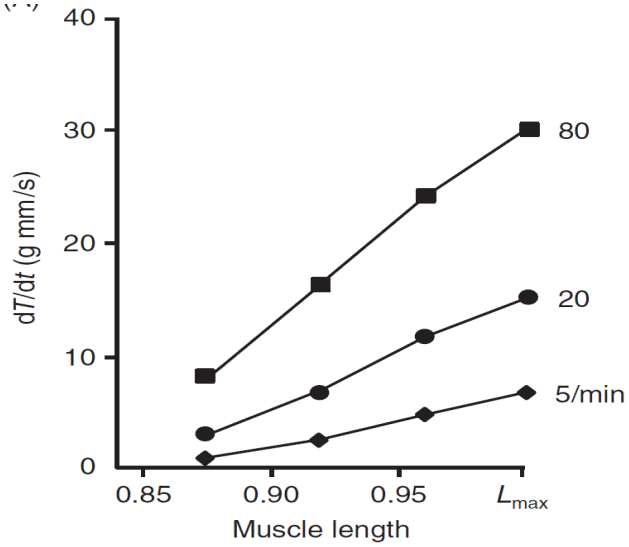
- The LV radius used in above calculations is the end-diastolic radius which is in turn proportional to the LVEDV. While being a measure of preload, LVEDV is also the volume of blood that must be compressed to generate the necessary force and pressure to open the aortic valve. Therefore, increase in LVEDV beyond the normal range of the Frank-Starling curve may cause a significant increase in LV afterload thereby leading to increased work and myocardial oxygen consumption.
- The LV pressure at the end of isovolumetric contraction phase is, by definition, the aortic diastolic pressure and thus, is an important part of the LV afterload and is used as a surrogate for its estimation
- Circumferential wall thickness is significantly affected by wall thickness and small changes in wall thickness would proportionally affect the LV afterload particularly in acute scenarios.

In chronic conditions, the same may act as a mechanical stimulus for hypertrophy of the cardiac muscles

This relationship is similar to that between afterload and velocity of contraction of cardiac muscles and thus, can be applied to assess myocardial contractility.

Effects of Heart Rate: Force-Frequency Relationship

Described as early as 1871 by Henry P. Bowditch, the "stair" or *treppe* is a phenomenon where incremental increases in stimulation frequency cause an increase in myocardial force development. The force-frequency relationship is a positive linear one under normal conditions. As can be seen in the graph plotted between cardiac muscle length and rate of tension developed in them, there is an upward and leftward shift of the curve consistent with increased inotropic effects as rate of stimulation is increased.



GRAPH 4: Force-Frequency Relationship

As has been discussed previously, an absolute increase in availability of Ca^{2+} will lead to an increase in the force developed during the contraction. This becomes possible due to increased Ca^{2+} sequestration in the SR by SERCA-2 which itself is made possible because of lesser time available for extrusion of Ca^{2+} across the sarcolemma as the frequency of excitation-contraction coupling increases with the increase in heart rate. It must also be borne in mind that these molecular events

become more dependent on active relaxation with higher frequency of stimulation. This relationship has been observed to be impaired in patients with LV failure.

With higher heart rates, myocardial oxygen demand and the utilisation of ATPs also show an increase. This predisposes the heart to myocardial oxygen demand and delivery mismatch especially in conditions with impaired oxygen delivery such as ischaemic heart disease.

LV Ejection Fraction

Perhaps the most well-known and commonly misinterpreted index of LV pump function is LVEF. Expressed as a percentage, it is the calculated ratio of LV stroke volume and LVEDV. It ranges from 65-75% in normal human subjects and is commonly used to represent degree of heart failure and response to therapeutic interventions. Like stroke volume, it is also affected by changes in load, contractile state of the heart and duration of cardiac cycle, thus getting affected by preload, afterload, myocyte contractility and heart rate respectively. Bring labile to the aforementioned conditions, measuring LVEF at a single point in time with prevalent loading conditions may not effectively represent the underlying myocardial contractile state. Also, its determination is based on the total stroke volume, which is directionless and allows for overestimation of LV performance in conditions like mitral regurgitation where stroke volume gets distributed between both aorta and LA.

LV Fractional Shortening

This is a computed index of cardiac function mathematically defined as

$$\frac{LV\ End\ Diastolic\ Length - LV\ End\ Systolic\ Length}{LV\ End\ Diastolic\ Length}$$

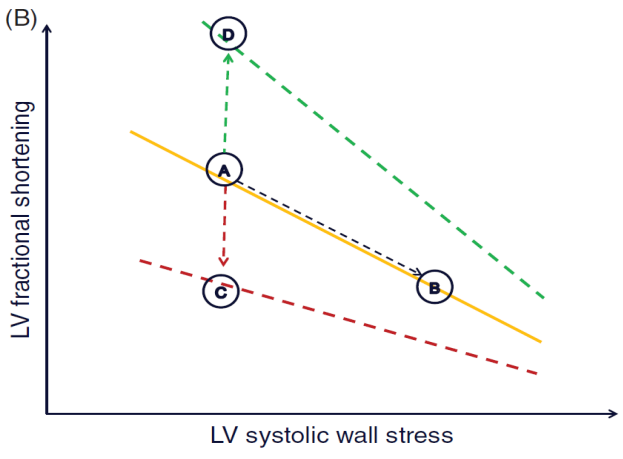
These dimensions are usually measured along the short axis of LV just below the papillary muscles.

Expressed as a percentage, its changes are observed to be directly correlated with ejection fraction in the normal heart with no significant heterogeneity in LV geometry. Variations in LV geometry due to pathological states such as MI may lead to wide variations between the LV fractional shortening and LV ejection fraction.

Velocity of Circumferential Fibre Shortening (Vcf)

Representing the extent of shortening of LV muscle fibres during ejection, Vcf is a calculated index based on LV dimensions and ejection times. It is also highly sensitive to changes in load conditions and heart rate. Therefore, relying on a single measurement instead of measuring Vcf with incremental changes in load conditions poses the risk of misinterpretation.

It stands to reason that since the above parameters are highly sensitive to afterload, observation of changes produced in these with measured, incremental changes in afterload would yield data with tangible assessment of myocardial function. The commonest approach is to plot fractional shortening or Vcf against LV end systolic wall stress. A schematic representation of such a plot is given below. The LV afterload is represented by LV systolic wall stress. As it increases between the points A to B, there is corresponding decrease in fractional shortening. This simply implies a change in LV afterload. If the graph shifts downward at an equivalent wall stress value (point C) this would indicate a fall in myocardial contractility, conversely, an upward shift (to point D) would imply an increase in the same.



GRAPH 5: Effect of Afterload on LVFS

While useful, this method does not allow us to evaluate effects of both preload and afterload simultaneously as it is still influenced by fluctuations in heart rate, autonomic responses and beat to beat changes in the stroke volume. For example, if stroke volume is reduced in one cycle, LVEDV would become higher for the next cardiac cycle leading to an increase in the stroke volume in that cycle.

Pressure-Volume Loop in assessment of LV Function

As described earlier, the pressure volume loop is a graphical representation of changes in these parameters during a cardiac cycle. The area contained within the loop is directly reflective of myocardial oxygen demand. Therefore, the loop can be used to represent the changes in systolic and diastolic functions of the LV with changes in both preload and afterload conditions. It also helps in evaluation of beat to beat variability, myocardial contractility and myocardial compliance.

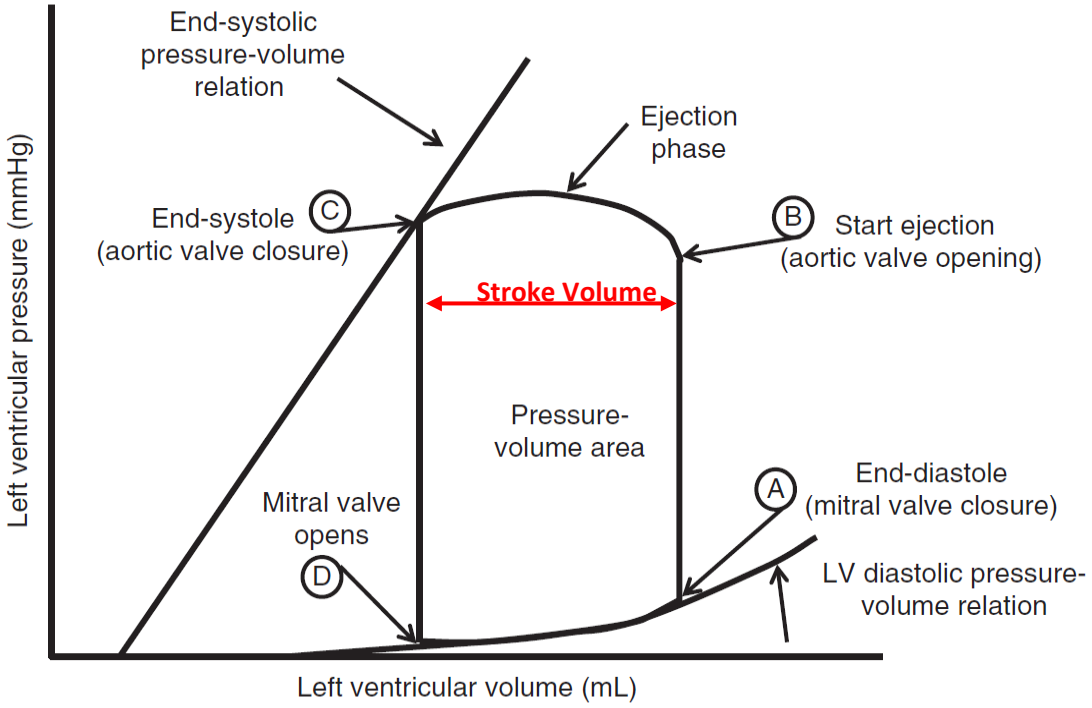
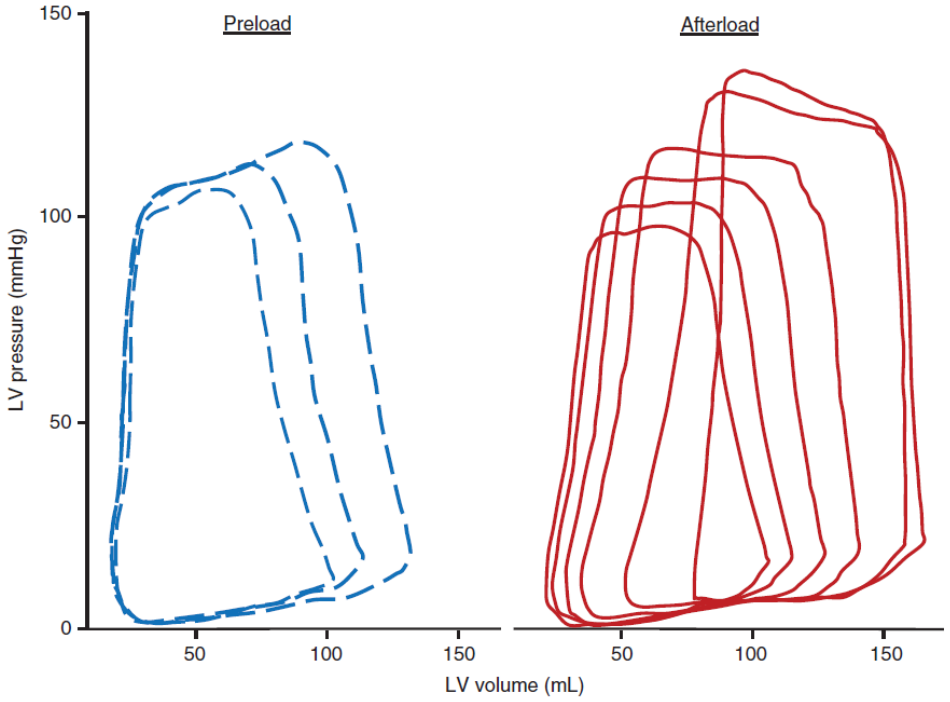


FIGURE 20: Pressure-Volume Loop in Assessment of LV Function

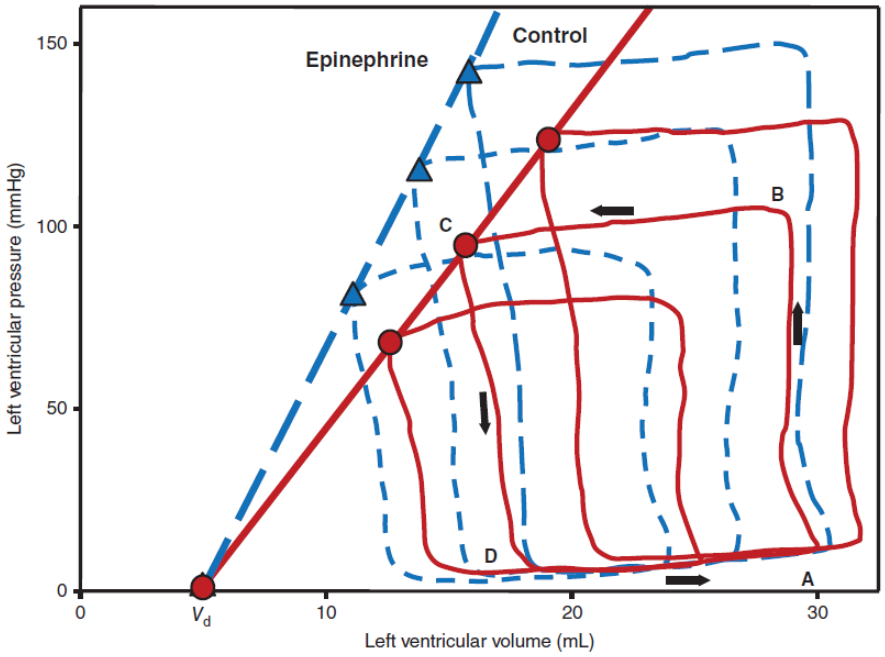


GRAPH 6: P-V Loop representation of Preload-LVEDV Relationship

As can be seen in the above schematic, acute changes in preload reflect as shifts of the end diastolic volume. An increase in preload will lead to an increased stroke volume causing an increase in the pressure volume area. With increase in afterload, stroke volume decreases initially leading to increased LVEDV for the subsequent beat. This higher preload eventually leads to normalisation of stroke volume. However, this happens with an increase in pressure-volume area indicating increased workload on the heart and thus increased myocardial oxygen demand.

LV End Systolic Pressure-Volume relationship

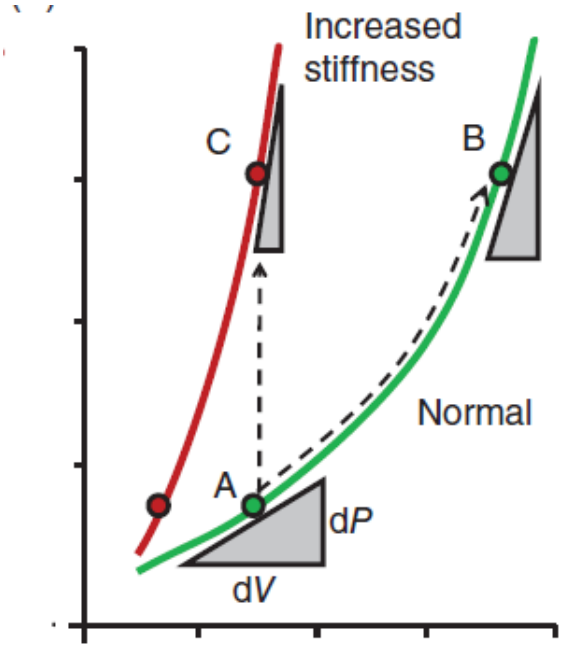
This refers to the linear relationship obtained by plotting LV end systolic pressure-volume points under various loading conditions and is reflective of the LV contractile state. An upward and leftward shift of the line indicates increased contractility. The slope of this line (E_{max}) represents the maximal ratio between LV pressure and volume and is perhaps the best way to assess myocardial contractility in intact physiological systems.



GRAPH 7: P-V Loop representation of Preload-LVESP Relationship

LV End Diastolic Pressure-Volume relationship

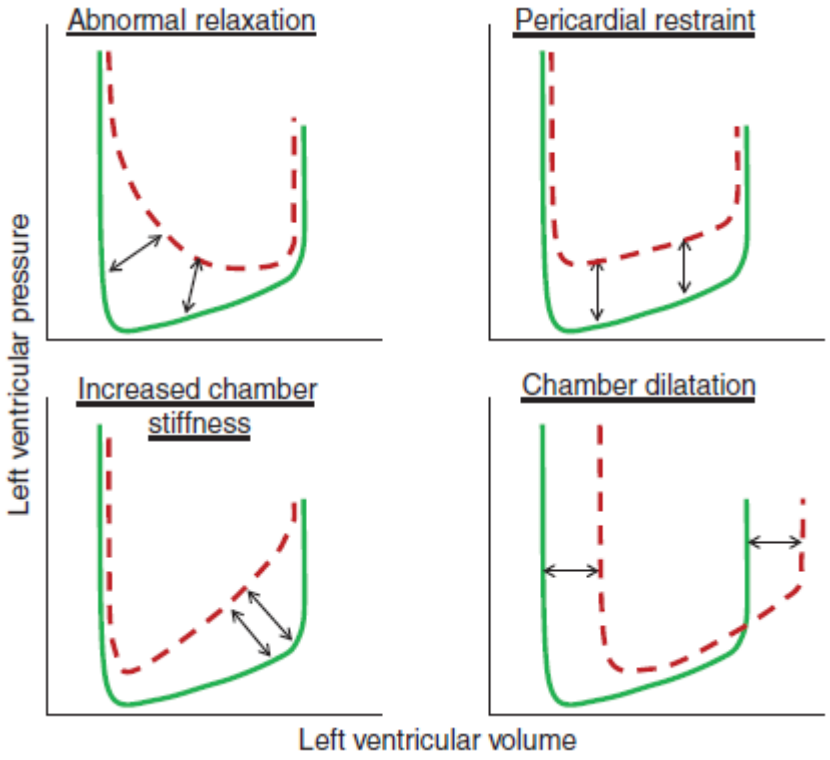
The PV loop also confers the advantage of helping us to assess the diastolic function. Similar to LVEDP-V relationship, LV end diastolic pressure and volume plots provide us with a curvilinear relationship reflecting the compliance of the LV. The differential of this curvilinear plot (dP/dV) is linear the slope of which represents the compliance of LV and is termed *modulus of chamber stiffness* (K_c).



GRAPH 8: LV End Diastolic Pressure-Volume relationship

Diastolic function of the LV is influenced by many factors and these must also be considered when interpreting the LVEDP-V relationship.

- Single measurement at one point of time cannot provide insights into LV diastolic function. A set of such values are required to be taken for appropriate interpretation
- *d*P/*d*V relationship can change with different operating volumes and pressures
- Structural and molecular factors also influence this assessment greatly



GRAPH 8: LV End Diastolic Pressure-Volume Changes in Different Pathologies

TABLE 2: Measurements and Indices of Cardiac Function

PRELOAD	• Pulmonary Venous Pressure • Left Atrial Pressure • LV End Diastolic Volume • LV End Diastolic Pressure • LV End Diastolic Wall stress
AFTERLOAD	• Aortic Diastolic Pressure • LV End Systolic Wall Stress
EJECTION PERFORMANCE	• Ejection Fraction • Stroke Volume • Velocity of circumferential fibre shortening – wall stress
LOAD INDEPENDENT INDICES OF LV FUNCTION	• Preload Recruitable Stroke Work • Velocity of circumferential shortening – wall stress • End Systolic Pressure-Volume relationship
CARDIAC OUTPUT	• Fick principle—equation: $$Q = \frac{V_{O2}}{Ca_{O2} - Cv_{O2}}$$ Q = cardiac output; V_{O2} = O_2 consumption Ca_{02} = arterial oxygen content Cv_{02} = mixed venous O_2 content • Indicator—thermodilution: $$Q = \frac{[V_i \times (T_b - T_i) \times 60 \times 1.08]}{A}$$ Q = cardiac output; V_i = volume of ejectate in mL T_b = blood temperature T_i = injectate temperature *1.08* = correction factor for specific gravity, specific heat of blood and indicator A = area under dilution curve multiplied by time required for inscription of the curve

	• Imaging approaches: $$Q = HR \times (EDV - ESV)$$ Q = Cardiac Output EDV = End-diastolic volume ESV = End-systolic volume HR = Heart rate

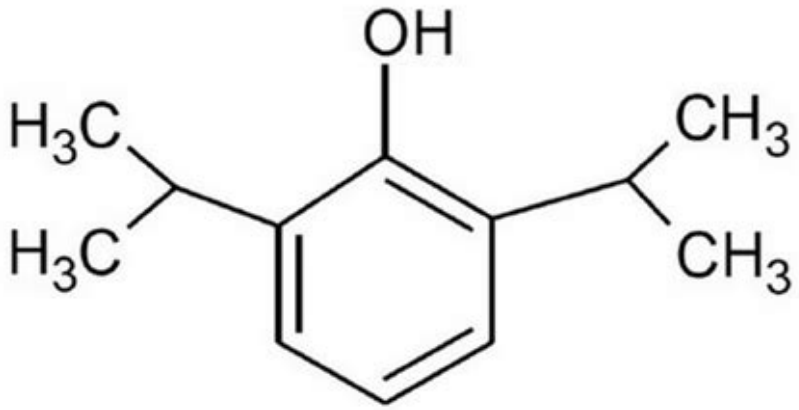
PHARMACOLOGY

PROPOFOL[37, 38, 40, 41, 59, 60]

Since its commercial launch in 1986 in Europe and 1989 in US, Propofol has surpassed thiopentone to become the most commonly used intravenous anaesthetic over the last three and a half decades. Rapid and smooth induction, nearly no excitation phenomena, low context sensitive half-life and low incidence of post-operative nausea and vomiting are some of the factors which have played a role in its wide acceptance.

Physiochemical properties

Also known as *Milk of Amnesia*, propofol is available as a slightly viscous, milky white liquid. An alkylphenol, it was initially investigated for its sedative properties in animals. The chemical structure is given below.



2,6 – diisopropylphenol

PROPOFOL

FIGURE 21

As an alkylphenol, it is highly lipid soluble and insoluble in aqueous solutions. After initial release in a formulation containing the surfactant Cremophor EL by Imperial Chemical Industries Limited (London, UK) it was quickly withdrawn due to high incidence of anaphylactic reactions arguably

due to the Cremophor. The commonly commercially available formulation contains propofol 1% (10mg/mL) as the active ingredient, soybean oil 10% (100mg/mL) as solvent, glycerol 2.25% (22.5 mg/mL) for tonicity and purified egg phosphatide or egg lecithin 1.2% (12mg/mL) as emulsifier. Bacterial contamination of the drug lead to the addition of preservatives to this formulation. EDTA 0.05 mg/mL was added to Diprivan® (AstraZeneca, London, UK) in 1996 which also required addition of sodium hydroxide to maintain pH (7-8.5). Generic preparations of propofol on the other hand, use sodium metabisulphite 0.25mg/mL as preservative and have a lower pH (4.5-6.4). Due to reports of pain on injection, other formulations containing more medium chain triglycerides were introduced. In this formulation free aqueous form of propofol, which is thought to be responsible for pain on injection by irritation of venous adventitia, is arguably reduced. These include Propoven® (Fresenius-Kabi, Bad Homburg, Germany) and Propofol-Lipuro® (B-Braun, Melsungen, Germany). All formulations commercially available are stable at room temperature, are not light sensitive, and may be diluted with 5% dextrose in water.

Pharmacokinetics

Absorption

Propofol is suitable only for intravenous use. Enteral routes have low bioavailability and high first pass metabolism along with high hepatic extraction ratio (> 90%). Also, it has an extremely bitter taste making oral formulations unpalatable.

Distribution

After intravenous administration, propofol is extensively bound to the plasma proteins (predominantly albumin) and erythrocytes. The free fraction is only 1.2–1.7%. Propofol readily crosses the blood–brain barrier (BBB) and causes rapid loss of consciousness within about one arm-brain circulation time. The speed of induction depends on patient related factors and speed of

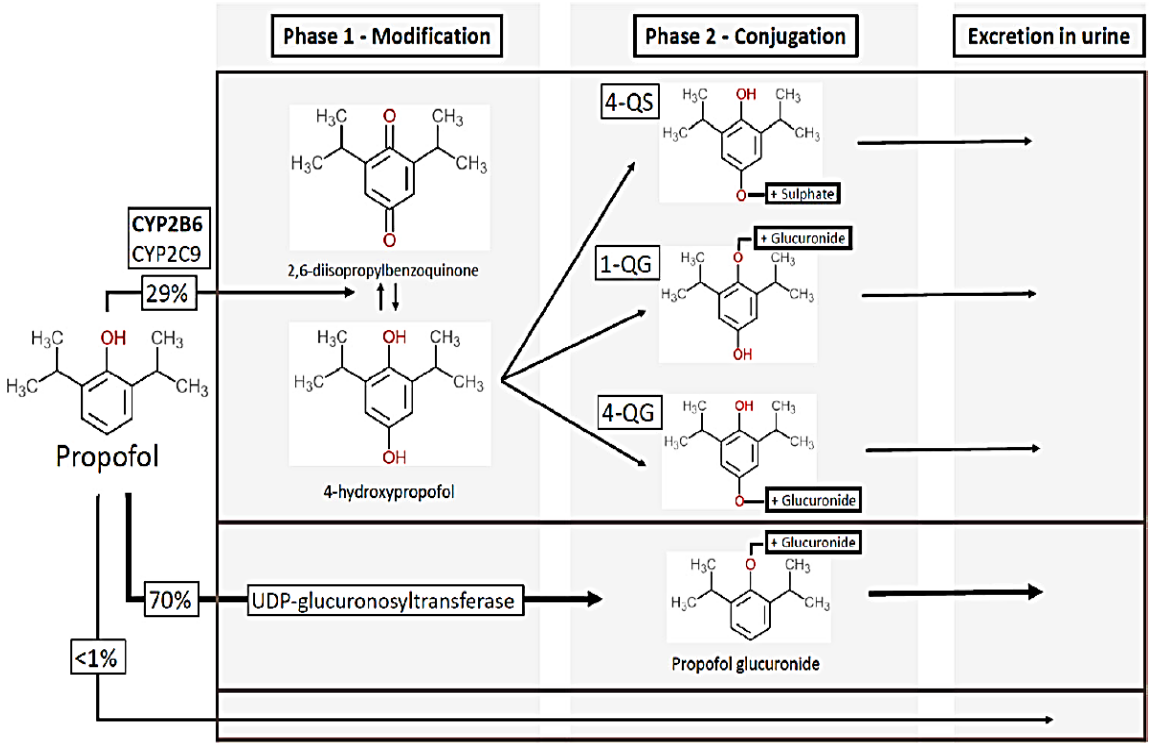
infusion. Free fraction of propofol in the CSF is approximately 31%. Placenta transfer is also fast and extensive, with mother to foetus plasma concentrations about 0.7 to 0.8. however, due to its clearance from the neonatal circulation, it has only minimal and short-lived clinical effects in unborn neonates and is thus safe for use during caesarean section.

After a single bolus, or short infusion, the time to offset of clinical effects is short because of the fast initial distribution. Redistribution to and from a slow compartment also occurs and is due to the high lipid solubility of propofol. even after prolonged administration, the offset of clinical effects is still reasonably fast compared with other intravenous hypnotics because redistribution of drug from the slow compartment is slow compared with the rates of metabolism and excretion. The context-sensitive half-life for propofol is thus generally favourable compared with other hypnotics. For a short infusion (< 3 hrs), the 80% decrement time is < 50 min, whereas for longer infusions (> 12 hrs) it increases up to 3.5 hrs.

Metabolism

Liver is the principal site of propofol metabolism where about 70% of the drug is conjugated with the help of cytochrome P450 isoforms. The major metabolites have no hypnotic activity. Due to a very high extraction ratio, propofol metabolism depends on hepatic perfusion maintenance. Fluctuations in hepatic blood flow cause increase or decrease in the rate of metabolism.

Extrahepatic sites contribute about 40% to metabolism of propofol. With an extraction ratio of about 60-70%, kidneys contribute to about one-third of propofol metabolism. Small intestines follow with an extraction ratio of about 24%. The role of lungs has been debatable so far although about 20-30% decrease in propofol concentration with an increase in its metabolites has been observed.



4-QS: 4-(2,6-diisopropyl-1,4-quinol)-sulphate a.k.a. 4-hydroxypropofol-sulphate
1-QG:1-(2,6-diisopropyl-1,4-quinol)-glucuronide a.k.a. 1-hydroxypropofol-glucuronide
4-QG: 4-(2,6-diisopropyl-1,4-quinol)-glucuronide a.k.a. 4-hydroxypropofol-glucuronide

FIGURE 22: Propofol Metabolism

Elimination and Excretion

After metabolism, 88% of propofol is excreted within 5 days in the urine. Less than 0.3% of administered propofol is excreted unchanged. Propofol is also excreted through exhalation. The amount of propofol excreted this way is extremely small (of the order of a few parts per billion), but the expired concentration correlates with plasma concentrations. B. Braun (Melsungen, Germany) has recently launched a commercially available and clinically certified spectrometer, capable of measuring propofol concentration in exhaled air.

The pharmacokinetics of propofol may be altered by various factors

- *Gender*: Women have a larger volume of distribution and higher clearance rates, but the elimination half-life is similar for males and females

- *Weight*:
    - The most important factors affecting PK in obese patients are changes in body composition, haemodynamics, regional blood flow, and liver and kidney function.
    - It is recommended to use Adjusted Body Weight (ABW) to determine dosage as per pharmacokinetic models.
- *Pre-existing Disease*
    - Hepatic disease: clearance is unchanged, but the elimination half-life is slightly prolonged, as is time to recovery. However, no dose adjustment required clinically. Extra-hepatic clearance may compensate for reduced hepatic function
    - Renal Disease: Does not affect propofol pharmacokinetics
- *Age*
    - Elderly individuals have decreased clearance rates and a smaller central compartment volume therefore, with increasing age, dose requirements are reduced
    - Children have a relatively larger central compartment volume (50%) and a more rapid clearance (25%). Hence, dose should be adjusted according to weight
    - Children younger than 3 years of age also show weight proportional pharmacokinetic parameters, but with larger central compartment and systemic clearance values than in adults or older children. Therefore, larger doses are required
- *Concomitant Medication*
    - Midazolam elevates the concentration of propofol particularly if used in a sedative dose. This seems to be a function of alteration in hepatic blood flow rather than competitive enzyme inhibition

- Propofol and opioids interact synergistically. This is more pronounced for analgesic drug effects (e.g. loss of response to noxious stimuli) than for hypnotic clinical endpoints. Fentanyl significantly decreases the propofol concentration required for loss of consciousness and suppression of responses to noxious stimuli. Sufentanil shows an additive interaction with propofol with respect to loss of responsiveness to verbal command during the induction of anaesthesia. It reduces the propofol concentration necessary for loss of responsiveness in a dose-dependent manner. Remifentanil shows showed a supra-additive interaction with propofol in regard to hypnotic and analgesic endpoints.

Pharmacodynamics

Central Nervous System

- **Hypnotic Effects**: Propofol exerts its hypnotic effect through potentiation of the effects of the inhibitory neurotransmitter GABA. It binds to the β-subunit of the postsynaptic $GABA_A$ receptor, where it causes an inward directed chloride current that hyperpolarizes the postsynaptic membrane and inhibits neuronal depolarization. This effect is dose-dependent. At low concentrations, propofol potentiates GABA-activated inward chloride currents, while at higher concentrations, it directly activates the channel opening. Propofol results also in widespread inhibition of the N-methyl-d-aspartate (NMDA) subtype of glutamate receptor through modulation of sodium channel gating, an action that also may contribute to the drug's CNS effects. Several brain areas play a crucial role in generation of consciousness and are affected by hypnotic drugs. Reticular formation of the brainstem where a number of sleep- and wakefulness-promoting cholinergic and monoaminergic nuclei that exert their effect by influencing higher cortical structures. Local inactivation of wakefulness-promoting areas, such as locus coeruleus and dorsal raphe, enhance anaesthesia, while local activation of various other wakefulness promoting areas, including

pontis oralis and centromedial thalamus, facilitate emergence from anaesthesia. One of the sleep-promoting nuclei is the ventrolateral preoptic area and its lesions enhance wakefulness. Hyperpolarization of thalamocortical neurons—and the resulting switching from a tonic firing state in wakefulness to a bursting firing state in unconsciousness—could be a final common pathway through which different hypnotics cause a disruption in thalamocortical and cortico-cortical loops, thereby causing unconsciousness. The cerebral cortex has long been identified as an important drug effect target for hypnotic drugs. The most consistent and largest changes occur in the frontal and posterior parietal cortex. These regions form part of a much wider 'default mode network', a functional network thought to be responsible for monitoring of internal environment in humans.

- **Amnesia:** Explicit memory seems to be most affected in a dose-dependent manner. The amnestic effects of propofol do not seem to be caused by interference with memory encoding. The exact neural mechanism of propofol induced amnesia in a conscious patient remains to be elucidated.
- **Anxiolysis:** Propofol produces anxiolysis in sub hypnotic doses. The sense of well-being in patients with propofol is related to the increase in dopamine concentrations in the nucleus accumbens (a phenomenon noted with drugs of abuse and pleasure-seeking behaviour). The exact mechanism of this anxiolysis is still not known, but inhibition of 5-HT activity in the hippocampus or nitric oxide synthase in the hypothalamus, amygdala and hippocampus may also be the mechanisms involved.
- **Analgesia:** Propofol has a direct depressant effect on neurons of the spinal cord. In acutely dissociated spinal dorsal horn neurons, propofol acts on $GABA_A$ and glycine receptors depressing ventral root potentials in the spinal cord elicited by monosynaptic reflexes or exposure of the spinal cord to substance P.
- **Antiemetic Effect:** Patients receiving anaesthesia with propofol experience significantly less PONV compared with that associated with other hypnotic drugs, irrespective of the use of adjunct drugs, patient characteristics or opiate use. This may be explained by the decrease

in serotonin levels it produces in the area postrema, probably through its action on GABA receptors. It has been demonstrated that propofol interacts with dopaminergic (D2) receptors in the chemoreceptor trigger zone, inhibits the limbic system, thereby interacting with cortical reflexes reaching the vomiting centre, and inhibits 5-HT3 receptors located in the central nervous system in a non-competitive and dose-dependent manner, thereby reducing the incidence and severity of PONV.

- **Neurophysiological Effects:** Propofol decreases cerebral blood flow, intracranial pressure, and cerebral metabolic rate, while maintaining dynamic and static autoregulation and vascular responsiveness to carbon dioxide. The evidence for neuroprotective effects of propofol during ischaemia-reperfusion injury is conflicting but it is still a part of multimodal neuroprotective regimens. It has also been shown to have both pro- and anti-convulsive activity.

Cardiovascular System

- **Blood Pressure:** The most prominent effect is systemic blood pressure reduction accompanied by a decrease in cardiac output. This effect is dose-dependent and even occurs at sedative doses. It is more pronounced in elderly and physiologically compromised patients. The effect is, at least partially, mediated by a significant decrease of sympathetic tone accompanied by a decrease in vascular resistance. Furthermore, propofol also inhibits the physiological baroreflex responses, thereby enhancing cardiovascular depression. The decrease in arterial blood pressure is associated with a decrease in cardiac output/cardiac index (±15%), stroke volume index (±20%), and systemic vascular resistance (15%-25%). Left ventricular stroke work index also is decreased (±30%). When looking specifically at right ventricular function, propofol produces a marked reduction in the slope of the right ventricular end-systolic pressure volume relationship. In patients with valvular heart disease, pulmonary artery and pulmonary capillary wedge pressure also are reduced, a finding that implies the resultant decrease in pressure is due to a decrease in preload and afterload.

- **Cardiac Contractility:** High concentrations of propofol abolish the inotropic effect of α- but not β-adrenoreceptor stimulation and enhance the lusitropic (relaxation) effect of β stimulation. Clinically, the myocardial depressant effect and the vasodilation are dose-dependent and plasma concentration dependent. The negative inotropic effect is mediated through a concentration-dependent decrease in the uptake of Ca^{2+} into the sarcoplasmic reticulum, which is simultaneously accompanied by an increase of myofilament sensitivity to Ca^{2+}, partially counteracting the effect.
- The haemodynamic response lags behind the hypnotic effect of propofol. While the hypnotic half-time plasma effect site equilibration time is 2.5 min, independent of age, haemodynamic half-time plasma effect site equilibration time is 5 min in young patients, and up to 10 min in elderly patients.
- In animal studies, high propofol doses caused dose-dependent attenuation of ischaemia-reperfusion myocardial injury (IRI) by exerting free radical scavenging effects and decreasing lipid peroxidase activity. These cardioprotective effects are less profound than those caused by sevoflurane.

Respiratory System

Propofol is a potent ventilatory depressant. It interferes with ventilation in a dose-dependent manner by affecting central chemoreceptor sensitivity, reducing ventilatory responses to hypercapnia and hypoxia. In higher doses, propofol causes apnoea. It also changes the pattern of breathing by decreasing the ribcage contribution to tidal volume by causing upper airway relaxation and suppression of upper airway reflexes. Furthermore, it attenuates vagal- and methacholine-induced bronchoconstriction and potentiates hypoxic pulmonary vasoconstriction.

Hepatorenal System

Despite the fact that the liver and kidneys are extensively involved in metabolism and excretion of propofol, their function does not appear to be affected by propofol. However, when cardiac output is not maintained, organ perfusion, and thus liver and renal perfusion, could be compromised.

Propofol infusion is known to cause green skin and urine discolouration caused by production of phenol green chromophore. Furthermore, urinary uric acid excretion is increased after propofol infusion, which can result in a cloudy appearance of the urine.

The administration of propofol is associated with the development of pancreatitis, which may be related to hypertriglyceridemia

Miscellaneous Effects

- Propofol does not enhance neuromuscular blockade produced by neuromuscular blocking drugs.
- Propofol does not trigger malignant hyperthermia and is an appropriate choice in patients with this condition
- After a single dose or a prolonged infusion it does not affect corticosteroid synthesis or alter the normal response to adrenocorticotropic hormone (ACTH) stimulation.
- Propofol in the emulsion formulation does not alter hepatic, hematologic, or fibrinolytic function.
- At sub-hypnotic doses, propofol relieves cholestatic pruritus and is likely as effective as naloxone in treating pruritus induced by spinal opiates.
- Propofol decreases polymorphonuclear leukocyte chemotaxis, but not adherence phagocytosis and killing. However, propofol inhibits phagocytosis and killing of *Staphylococcus aureus* and *Escherichia coli.*

Indications, Contraindications and Adverse Effects

Indications

- **Induction of anaesthesia:** The intravenous induction dose is 1 to 2.5 mg/kg. Physiologic characteristics that best determine the appropriate dose to induce anaesthesia are age, lean body mass, and central blood volume. Premedication with an opiate or a benzodiazepine, or both, markedly reduces the necessary induction dose. The induction dose needs to be reduced in elderly patients while it is increased in paediatric age group owing to pharmacokinetic differences. To prevent hypotension in sicker patients or in patients presenting for cardiac surgery, intravenously administered fluids should be given as tolerated, and propofol titrated to achieve the desired anaesthetic state. Propofol, when used for induction of anaesthesia in short-lasting procedures, results in a significantly quicker recovery and an earlier return of psychomotor function compared with thiopental or methohexital, regardless of the anaesthetic used for maintenance of anaesthesia.
- **Maintenance of anaesthesia:** The knowledge of blood levels of propofol required for loss of consciousness (2.5 to 4.5 μg/mL) and surgery (2.5 to 8 μg/mL) and of the pharmacokinetics of propofol has enabled the use of pharmacokinetic model–driven infusion systems to deliver propofol as a continuous infusion for the maintenance of anaesthesia. Using reduced and titrated doses of propofol for induction of anaesthesia and titrated infusion rates of 50 to 200 μg/kg/min combined with an opioid for maintenance, propofol provides intraoperative hemodynamic control and ischemic episodes similar to those with either enflurane/opioid or a primary opioid technique for cardiovascular surgeries.
- **Sedation:** Propofol has been evaluated and used extensively for sedation during surgical procedures and mechanical ventilation in the ICU. Infusion rates required for sedation to supplement regional anaesthesia in healthy patients are half or less than the rates required for general anaesthesia (i.e., 30-60 μg/kg/min). The pharmacokinetic profile of propofol makes it suitable for prolonged sedation as well. In both scenarios however infusions should be individually titrated to desired effect. Long term infusions should always consider the

hemodynamic side effects, tolerance, and rare occurrences of hypertriglyceridemia (and potential pancreatitis) or propofol infusion syndrome. Maintaining the smallest possible dose required for the desired level of sedation with potential "sedation holidays" should be considered as part of a long-term propofol sedation regimen. The recommended maximal dose of propofol infusion rate is 80 μg/kg/min (<5 mg/kg/h).

- **Antiemetic:** Can be used in a dose of 10-20mg IV which may be repeated after 5-10 min. It can also be used as an infusion 10 μg/kg/min.

Contraindications

- Patients with hypersensitivity to propofol or any of the components of its formulation
- Patients with fat metabolism disorders

Adverse Effects

- Pain on injection: reduced by using a large vein, avoiding veins in the dorsum of the hand, and adding lidocaine to the propofol solution or changing the propofol formulation.
- Loss of airway reflexes, hypoventilation and apnoea
- Hypotension
- Neurotoxicity in paediatric patients leading to cognitive impairment
- Propofol Infusion Syndrome (PRIS): Comprises of severe metabolic acidosis, rhabdomyolysis, hyperkalaemia and cardiovascular collapse. Although rare, it is usually seen in patients receiving propofol infusion > 4mg/kg/hr for more than 48 hours. The clinical features of propofol infusion syndrome are
    - Acute refractory bradycardia leading to asystole, in the presence of one or more of
        - Metabolic acidosis (base deficit >10 mmol/ L−1),
        - Rhabdomyolysis,
        - Hyperlipidaemia, and
        - Enlarged or fatty liver.

- Cardiomyopathy with acute cardiac failure,
- Skeletal myopathy,
- Hyperkalaemia,
- Hepatomegaly, and lipemia.

The symptoms and signs are the result of muscle injury and of the release of intracellular toxic contents.

The major risk factors for its development are

- Poor oxygen delivery,
- Sepsis,
- Serious cerebral injury, and
- Large propofol dosage.

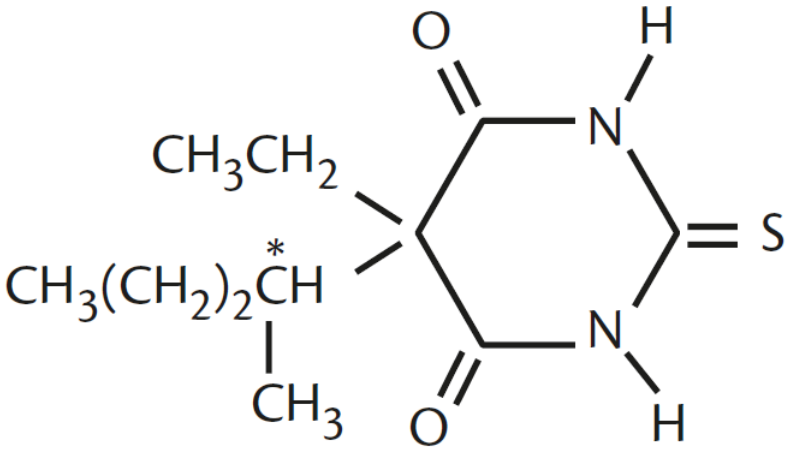
Predisposing factors for the propofol infusion syndrome are likely genetic disorders impairing fatty acid metabolism, such as medium-chain acyl CoA (MCAD) deficiency and low carbohydrate supply.

THIOPENTONE[37,38, 40, 42, 59, 60]

After the clinical introduction of thiopental by Waters and Lundy in 1934, thiopental became preferred clinically because of its rapid onset of action and short duration, without the excitatory effects of hexobarbital. It has remained the gold standard against which all other anaesthetic agents were compared. While it is not available in US since 2011, it remains available in many other countries as it is tried, tested and cost effective.

Physiochemical Properties

Barbiturates are formed through the 'interaction' of malonic acid and urea to form the barbiturate ring structure. Thiopental is a thiobarbiturate which have a hydrogen at N1 and sulphur at C2. It has an asymmetric carbon atom at C5, and therefore is a racemic mixture of two enantiomers.



5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid

THIOPENTONE

FIGURE 23

Thiopental is a weak base (pKa 7.45– 7.6 at 25– 27°C). It is almost insoluble in aqueous media, with an oil/ water partition coefficient around 60:1. This causes a high lipid solubility and low degree of

ionisation at physiological pH. These factors are responsible for its rapid uptake across the blood-brain barrier.

Thiopental is formulated as a pale-yellow powder to which 6% anhydrous sodium carbonate is added in an ampoule containing an inert atmosphere of nitrogen. Although poorly soluble in water, thiopental dissolves in the alkaline solution of the sodium carbonate, where a 2.5% solution has a pH of 10.5. There is no added preservative, but the alkaline solution is bacteriostatic. This solution will cause significant tissue damage if administered accidentally outside the vein or in an artery. Thiopental should not be dissolved in Ringer's lactate, as this decreases the alkalinity of the solution and reduces thiopental solubility leading to the risk of precipitation of the free acid. The solution in water or saline is stable when kept at 4°C for well over 7 days. The usual recommended dilution for thiopental is 2.5% in adults and 1% in children to limit the consequences of an accidental extravascular injection. Examples of drugs that are not to be co-administered or mixed in solution with the barbiturates are atracurium, vecuronium, rocuronium, suxamethonium, alfentanil, sufentanil, dobutamine, dopamine, esketamine, and midazolam. Mixing of thiopental with vecuronium or pancuronium results in the formation of a precipitate that may occlude the IV line during a rapid sequence induction of anaesthesia.

Pharmacokinetics

Absorption

Thiopentone is primarily used intravenously. Rectal administration has also been used to produce deep hypnosis implying rapid absorption from this site. Orally administered thiopentone is also rapidly absorbed especially if stomach is empty and drug is in solution. The rate of thiopental absorption is probably influenced by its lipid and aqueous solubilities. Thiopental, undissociated in the acidic gastric contents, is readily absorbed by passive diffusion.

Distribution

Thiopental is extensively bound (about 80%) to plasma albumin. This binding has been described as non- linear, with the possibility of a greater unbound fraction and therefore an enhanced effect at high concentrations. However, studies have shown this binding to be linear in nature over the concentration range expected after an induction dose. The simultaneous administration of drugs which might compete with thiopental for albumin binding sites does not lead to clinically significant changes in the unbound fraction.

After intravenous injection, thiopental is distributed to the various tissues according to their local blood flow, tissue partition coefficients, and blood– tissue concentration gradients. The brain is initially exposed to high thiopental concentrations because of its high blood flow and the lipid solubility of the drug. Blood– brain equilibration is rapid, explaining the rapid onset of effect. Other peripheral tissues are also exposed to thiopental at an early stage; but as their volume of distribution is high and their regional blood flow is proportionally lower, thiopental concentrations in these tissues increase more slowly, and continue to increase while brain concentrations are already decreasing. This explains both how thiopental has a rapid onset and short duration of effect after a bolus dose, and how it may accumulate after an infusion.

Metabolism

Thiopentone is metabolised and eliminated via the liver with very little renal involvement. The metabolites are almost all inactive, water-soluble, and excreted in the urine. Pentobarbital is a major and pharmacologically active metabolite of thiopental and contributes to the prolonged effects of large or repeated doses. Metabolism of thiopentone takes place through four processes:

- Oxidation of the aryl, alkyl, or phenyl moiety at C5: This is the most important pathway, producing polar (charged) alcohols, ketones, phenols, or carboxylic acids. These metabolites are readily excreted in the urine or as glucuronic acid conjugates in the bile.

- N-dealkylation
- Desulphuration of the thiobarbiturates at C2
- Destruction of the barbituric acid ring: Hydrolytic cleavage of the barbituric acid ring forms a minimal contribution to the total metabolism of barbiturates, since the ring is stable in vivo.

Drugs that induce oxidative microsomes or long-term administration enhance the metabolism of barbiturates. The hepatic enzyme induction by barbiturates is the reason that they are not recommended for administration to patients with acute intermittent porphyria. Barbiturates may precipitate an attack by stimulating γ-aminolevulinic acid synthetase, the enzyme responsible for the production of porphyrins.

Elimination and Excretion

Thiopentone metabolism is slow and depends on liver enzyme activity and, to a lesser extent, changes in protein binding. The amount of drug excreted unchanged in urine is trivial.

The hepatic extraction ratio is less than 20% and the clearance during the elimination phase is modest (250 mL/min). As a consequence, thiopental clearance is dependent on intrinsic clearance and independent of hepatic blood flow. This produces a long and context-dependent elimination half-life and hence makes thiopentone unsuitable for maintenance of anaesthesia.

In usual doses (4-5 mg/kg), thiopental exhibits first-order kinetics (i.e., a constant fraction of drug is cleared from the body per unit time). High thiopental blood concentrations saturate the capacity of the hepatic P450 cytochromes and metabolism reaches a ceiling "zero order" fixed rate. This occurs at concentrations required for EEG burst suppression (50-60 (μg/mL), which have been used in clinical practice in uncontrolled status epilepticus and for putative cerebral protection, but are much greater than required for anaesthesia.

Many factors may influence the pharmacokinetics of thiopentone

- *Gender:* The volume of distribution is slightly larger in female patients, causing a longer elimination half-life. However, this difference is not observed in the elderly age groups.
- *Age:*
    - Required induction doses of thiopentone are reduced in the elderly age group owing to a reduction in the volume of distribution. This is also attributed to increase in the volume of slowly equilibrating compartment depending on the pharmacokinetic model used. Clearance of the drug appears to be unaffected.
    - In children > 5 months and adults, volume of distribution shows no changes but the elimination is accelerated in children. Thus, recovery times may be faster for infants.
    - In neonates, elimination half life is longer due to reduced clearance probably due to immaturity of the hepatic enzyme systems.
- *Obesity:* Because of the large apparent volume of distribution, there is a prolongation of elimination half-life.
- *Pregnancy:* High clearance of the drug is seen due to induction of hepatic microsomal enzymes by progesterone. Along with this there is an increase in volume of distribution leading to longer elimination half-life.
- *Disease states:*
    - Alcoholism: Increased plasma clearance possibly due to activation of hepatic mono-oxygenase system
    - Hepatic Failure: While decreased albumin concentrations lead to higher fraction of unbound drug, total plasma clearance is unchanged. This is explained by the decrease in the capacity of the liver to metabolise the unbound drug
    - Renal Failure: Volume of distribution in equilibrated tissues increases which is offset by increase in total clearance. Consequently elimination half-life is not changed

- *Concomitant Medication:*
    - β- adrenergic blockers may modify early drug distribution through a reduction in cardiac output
    - Halothane, enflurane and nitrous oxide do not affect the distribution or clearance of thiopentone.
    - Heparin does not influence thiopentone binding
    - Surgical stress does not inhibit thiopentone metabolism due to corticosteroid release.

Pharmacodynamics

Mechanism of Action

The mechanisms of action of barbiturates on the CNS are largely unknown, with the exception of their action on the $GABA_A$ receptor. The actions are classified into two types

- **Enhancement of the synaptic actions of inhibitory neurotransmitters**
    - Thiopentone binding to the $GABA_A$ receptor enhances and mimics the action of GABA by increasing chloride conductance through the ion channel. This causes hyperpolarization of the cell membrane and increases the threshold of excitability of the postsynaptic neuron.
    - At low concentrations barbiturates enhance the effects of GABA, decreasing the rate of dissociation of GABA from its receptor and increasing the duration of GABA-activated chloride ion channel openings. This enhancement of the action of GABA is likely responsible for the sedative-hypnotic effects of the barbiturates.
    - At larger concentrations, the barbiturates activate the chloride channels directly, without the binding of GABA, acting as the agonist itself. The GABA-mimetic effect at slightly higher concentrations may be responsible for what is termed barbiturate anaesthesia.

- **Blockade of the synaptic actions of excitatory neurotransmitters**
    - Inhibition of the synaptic transmission of excitatory neurotransmitters, such as glutamate and acetylcholine.
    - Thiopentone may exert GABA-independent effects on the glutaminergic-NMDA system.

Central Nervous System

- Thiopental depresses $CMRO_2$, in a dose-dependent manner, to a maximum of 55% of conscious levels when the EEG becomes flat leaving all metabolic energy for the maintenance of cellular integrity.
- Reduced $CMRO_2$ causes cerebral vasoconstriction and increased cerebral vascular resistance reducing cerebral blood flow and intracranial pressure (ICP).
- Cerebral perfusion pressure (CPP) is usually maintained or slightly elevated. This is because the CPP equals MAP minus ICP. In this relationship, ICP decreases more than MAP after thiopentone administration, preserving CPP.
- Thiopentone produces dose-dependent CNS depression ranging from sedation to general anaesthesia when administered as bolus injections. As the dose of thiopental over the same time is increased, an increased percentage of patients will be anaesthetised.
- Awakening may be delayed in older patients because of increased CNS sensitivity, alterations in metabolism, or decreased central volume of distribution relative to younger adults
- Thiopentone does not produce analgesia; instead, some evidence suggests it may reduce the pain threshold causing hyperalgesia at lower concentrations.

Cardiovascular System

- Thiopentone causes Cardiovascular depression as a result of central and peripheral (direct vascular and cardiac) effects.
- Hemodynamic changes are dependent on the infusion rate of thiopentone. In the dose ranges studied so far, no relationship between plasma thiopental level and hemodynamic effect has been found.
- The primary cardiovascular effect during induction of anaesthesia is peripheral vasodilation causing a pooling of blood in the venous system leading to a reduction in preload
- There is a decrease in cardiac output due to
    - Direct negative inotropic action, due to a decrease of calcium influx into the cells,
    - Decreased ventricular filling, due to increased capacitance, and
    - Transiently decreased sympathetic outflow from the CNS.
- Systemic vascular resistance and arterial blood pressure remain relatively unaltered as does cardiac index following a normal induction dose in healthy patients.
- There is an increase in heart rate probably resulting from the baroreceptor-mediated sympathetic reflex stimulation of the heart in response to the decrease in output and pressure. This is potentially deleterious because of the obligatory increase in myocardial oxygen consumption that accompanies the increased heart rate.
- It has been shown to prolong the QT interval in animal studies
- Thiopentone must be used cautiously in patients for whom an increase in heart rate or a decrease in preload might be detrimental, for example those with hypovolemia, critical coronary artery disease, ventricular hypertrophy, or heart failure.

Respiratory System

- Thiopental produces dose-dependent ventilatory depression, and apnoea usually follows an induction dose.

- Responses to hypoxia and hypercapnia are also depressed for a prolonged period.
- Laryngeal and tracheal reflexes are depressed to a lesser degree than by equipotent anaesthetic doses of propofol.
- Laryngospasm and bronchospasm may be related to insertion of artificial airways, laryngeal masks, or tracheal tubes in lightly anesthetized patients.
- Although safe in asthmatic patients, it does not cause bronchodilation.
- The ventilatory pattern with thiopental induction has been described as "double apnoea," that is an initial apnoea of a few seconds occurring upon drug administration, succeeded by a few breaths of reasonably adequate tidal volume, which is followed by a more prolonged period of apnoea, typically of approximately 25 seconds. This apnoea occurs in at least 20% of cases.

Miscellaneous Effects

- Inhibition of phagocytic activity of leucocytes
- Dose related suppression of human leucocyte activation
- However, no clinically apparent effect regarding above two has been demonstrated so far.

Indications, Contraindications and Adverse Effects

Indications

- **Induction of Anaesthesia:** Thiopental is an excellent drug to use for induction of anaesthesia in doses of 3-7 mg/Kg. The prompt onset (15-30 seconds) of action and smooth induction are advantages for this drug. The rapid emergence, particularly after single use for induction, is also a reason for the widespread use of thiopental in this setting.

- **Maintenance of Anaesthesia:** Thiopental can be used to maintain general anaesthesia because repeated doses reliably sustain unconsciousness and contribute to amnesia but should not be the drug of first choice as the hypnotic component in balanced anaesthesia.
- **Refractory Seizures:** Thiopental remains the most effective drug for controlling status epilepticus refractory to benzodiazepines and specialized anticonvulsant drugs. As a consequence of interactions with these drugs and prolonged seizure activity, airway protection, assistance of ventilation, support of the circulation, and transfer to an intensive care unit are usually necessary.

Contraindications

- Respiratory obstruction or an inadequate airway, thiopentone may worsen respiratory depression
- Severe cardiovascular instability or shock contraindicate its use
- Status asthmaticus is a condition in which airway control and ventilation may be worsened
- Porphyria: It is a potent inducer of δ-aminolevulinic acid synthetase and can precipitate attacks of acute intermittent or variegate porphyria in susceptible patients.
- Without proper induction equipment (IV instrumentation) and airway equipment (means of artificial ventilation), thiopentone should not be administered.

Adverse Effects

- Garlic or onion taste (40% of patients),
- Allergic reactions – IgE mediated
- Pain on injection into small veins and local thrombophlebitis
- Local tissue irritation, and rarely, tissue necrosis.

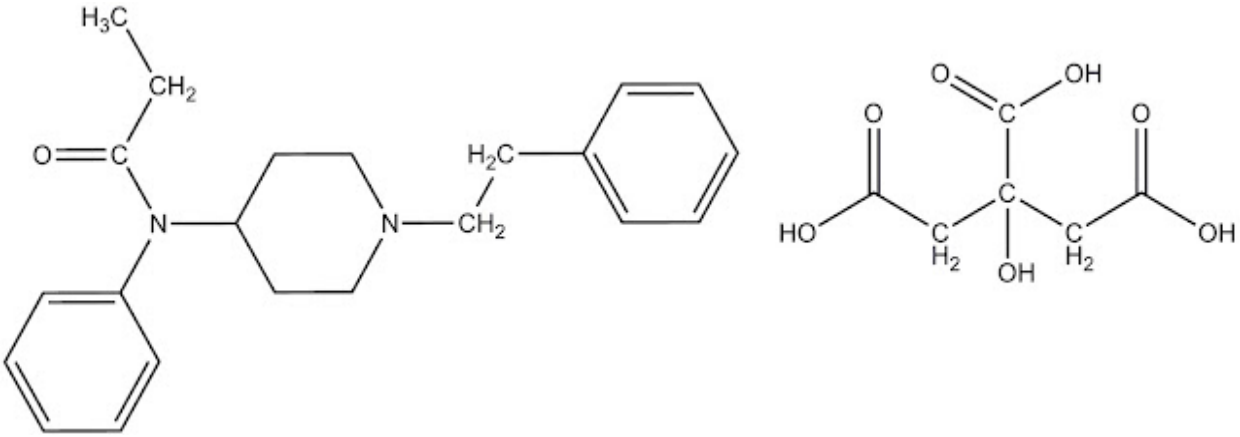
- Accidental intra-arterial injection can be much more serious. Intense and painful arterial spasm and chemical arteritis can lead to irreversible thrombosis. Immediate treatment with saline is necessary to dilute the barbiturate with local anaesthetic block of somatic and sympathetic innervation, to relieve vascular spasm and pain, and with heparin anticoagulation to inhibit thrombosis.
- A transient urticarial rash may develop on the head, neck, and trunk due to dose dependent release of histamine
- More severe reactions such as facial oedema, hives, bronchospasm, and anaphylaxis can occur.
- Involuntary excitatory movements, hypertonus, coughing, and hiccupping.

FENTANYL[37-40, 43, 44, 59, 60]

First synthesized by Dr. Paul Janssen and the Janssen Company of Beerse, Belgium, in 1960, fentanyl has become the most often used intravenous opioid for intraoperative analgesia following its introduction in Europe in 1963 and in the United States in 1968. As an analgesic, it is 75-125 times more potent than morphine. Its successful use in cardiac and vascular surgeries in 1970s and early 1980s along with the fact that it is easy and inexpensive to produce lead to a great boom in its usage especially after the branded drug lost its patent.

Physiochemical Properties

The first of the 4-anilinopiperidine series of opioid agonists, fentanyl is a chemical congener of the reversed ester of pethidine (meperidine). It is also the first synthetic opioid produced and accepted into clinical practice.



N-(1-phenethylpiperidin-4-yl)-N-phenylpropionamide 2-hydroxypropane-1,2,3-tricarboxylate

FENTANYL CITRATE

FIGURE 24

Fentanyl is prepared as a colourless solution for injection containing 50 µg/ml, as transdermal patches that release between 25 and 100 µg per hour for 72 hours and as lozenges releasing 200 µg–1.6 mg over 15 minutes. The pKa of fentanyl is 8.4 and it is 9% unionized at a pH of 7.4. It is much more

lipid soluble as compared to morphine. This facilitates its passage across the blood brain barrier and is also responsible for the higher potency and faster action than morphine. Consequently, plasma concentrations of fentanyl (unlike morphine) correlate well with CSF concentrations. Fentanyl is also rapidly redistributed to inactive tissue sites such as fat and skeletal muscles, with an associated decrease in the plasma concentration of the drug. This rapid redistribution is also responsible for the shorter duration of action of fentanyl.

Pharmacokinetics

Absorption

Fentanyl is primarily used intravenously in anaesthetic practice apart from epidural injection for induction or supplementation of general anaesthesia. Transdermal patches are mainly used in the post-operative period for pain management. Other formulations include oral tablets, lozenges, buccal films, sublingual tablets and intranasal and sublingual sprays. While the sprays can be administered within seconds, other forms require between five to thirty minutes for administration alone. Onset of action takes 5-15 minutes for all non-injectable forms with a bioavailability between 50-70 %. In contrast with intravenous injections rapid onset of action is seen due to its lipid solubility.

Distribution

On intravenous injection, fentanyl is immediately diluted and bound to proteins in the plasma compartment. This binding is pH dependent with the drug more ionised in acidic environments. The lungs exert a significant first-pass effect and transiently take up approximately 75% of an injected dose of fentanyl. Plasma concentrations fall rapidly after injection due to distribution to the peripheral compartments and rapid and extensive uptake by the tissues. This leads to rapid equilibration with brain and other vascular rich tissues. Despite the clinical impression that fentanyl produces a rapid onset, there is a distinct time lag between the peak plasma fentanyl concentration and peak slowing

on the EEG. This delay reflects the effect site equilibration time between blood and the brain for fentanyl, which is 6.4 minutes. More than 80% of the injected dose leaves the plasma in < 5 minutes. The plasma concentrations of fentanyl are maintained by slow reuptake from inactive tissue sites, which accounts for persistent drug effects. This is also a function of its high lipid solubility as it rapidly passes into tissues compared with the less lipid-soluble morphine. Additionally, intrathecal fentanyl does not cause delayed respiratory depression, unlike morphine, as, due to its high lipid solubility, it is rapidly absorbed into the spinal cord.

Metabolism

As is the case with most lipophilic drugs, fentanyl is almost completely metabolised in the liver with only small amounts being excreted unchanged in urine. Fentanyl undergoes phase I metabolism in the liver primarily by oxidative N-dealkylation to norfentanyl. Both fentanyl and norfentanyl then undergo further hydroxylation to hydroxypropionyl derivatives. The drug may also undergo hydroxylation and amide hydrolysis. Metabolism is dependent upon human cytochrome P450 (CYP3A4) isoenzyme system. Through this the inactive metabolites are produced and eventually excreted in the urine. Metabolites begin to appear in the plasma as early as 1.5 minutes after injection.

The cytochrome P450 system is also present in the walls of the intestines where the drug may be presented due to entero-systemic recirculation and first-pass metabolism particularly on oral administration. Subsequent enteral absorption of the drug may be part of the reason for development of *secondary peaks* of plasma concentration.

Elimination and Excretion

The hepatic extraction ratio for fentanyl is 80-100% and it is metabolised in the liver to produce pharmacologically inactive compounds which are excreted in urine. Less than 10% of an administered dose is excreted in the urine. The clearance of fentanyl is 10-20 ml/kg/min. The terminal elimination half life is prolonged between 20 minutes to 8 hours. This is due to slow reuptake from the vascular tissues particularly after prolonged infusions. The volume of distribution is about 4L/Kg which is higher than that of morphine and explains the prolonged elimination half-life.

Pharmacokinetics of fentanyl is also affected by multiple factors:

- *Age:*
    - The plasma concentrations are significantly lower in infants and children on administration of equipotent doses when compared to adults despite higher values observed after bolus injections. This is possibly related to
        - Larger volume of distribution
        - Larger average lipid concentration
        - Larger free plasma fraction
        - Decreased hepatic blood flow
        - Limited enzyme function
    - The elderly patients require less opioid analgesics than young and middle-aged adults, who, in turn, require less than small children to achieve the same clinical effect.
    - In the elderly, lower dosage requirements are possibly due to pharmacodynamic effects as studies have found no difference in fentanyl pharmacokinetics among the young and elderly

- *Obesity:* Amount of fat in the body affects lipophilic drugs like fentanyl. A higher fat content may result in a larger volume of distribution at steady-state and a longer elimination half-life.
- *Plasma Protein Content:* As fentanyl is highly protein bound (to α_1-acid glycoprotein), it is reasonable to assume that with decrease in its concentration, higher fraction of free drug would be available and thus reduced dosages may be required. Decreases in α_1-acid glycoprotein can occur with pregnancy, dilution of plasma proteins, in intensive care and trauma patients, during cardiopulmonary bypass and other physiological stresses. Some diseased states like myocardial infarction may cause an increase in the same while others like liver cirrhosis affect the binding affinity. Although it would be better to err on the side of caution and titrate dosages to clinical effect.
- *Acid-Base Status:* There is an increase in protein binding with alkalosis and a decrease with acidosis. In other words, unbound fraction of fentanyl, increases with decreasing pH.
- *Pre-existing Diseases*
    - *Liver Disease:* The degree of liver dysfunction as well as the ability of the drug to bind to plasma proteins are important variables in fentanyl pharmacokinetics. Due to its high hepatic clearance, fentanyl metabolism is sensitive to changes in hepatic blood flow. Diminished hepatic enzymes and decreased fraction of plasma protein bound drug also affect its actions.
    - *Renal Disease:* Renal insufficiency does not appear to alter significantly the fundamental pharmacokinetic properties of fentanyl following bolus administration. However, continuous administration as in ICUs could lead to an increased magnitude and duration of the effect.
- *Cardiopulmonary Bypass:* It affects fentanyl pharmacokinetics greatly
    - Membrane oxygenator-mediated uptake can lead to reduced plasma concentrations of fentanyl

- Haemodilution causes increase in the initial volume of distribution and a marked decrease in plasma concentration. It also lowers plasma protein levels as well as drug binding, resulting in increased unbound drug fraction.
- Hypotension decreases hepatic blood flow, resulting in a reduced clearance of fentanyl
- Hypothermia decreases enzymatic hepatic activity and increases the elimination half-life of fentanyl.

- *Concomitant Drugs:* When given concurrently with other drugs that affect CPY3A4 activity, potential increase in fentanyl plasma concentrations can rise or prolong its activity. CYP3A4 inhibitors such as certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, and verapamil may result in an increase in fentanyl plasma concentration sufficient to cause potentially fatal respiratory depression.

Pharmacodynamics

Mechanism of Action

Fentanyl is a highly selective μ-agonist (or MOP agonist). The MOP receptor appears to be specifically involved in the mediation of analgesia. It appears to exert its effects by interacting with presynaptic Gi-protein receptors, leading to hyperpolarization of the cell membrane by increasing K^+ conductance. It also causes inhibition of adenylate cyclase which leads to reduced production of cAMP, and closure of voltage-sensitive calcium channels as well. This results in a decrease in membrane excitability that eventually may decrease both pre- and post-synaptic responses.

The receptors through which opioids like fentanyl act and the physiological effects mediated by those receptors are summarised in the given table on the next page.

Biased agonism refers to the phenomenon of differential activation of G-protein–coupled cell signalling pathways producing divergent physiologic outcomes. This has been used to explain unwanted side effects of opioids like addiction, respiratory depression and GI effects.

TABLE 3: Opioid Receptors and Action

	μ	κ	δ	Nociceptin
Analgesia				
Supraspinal	+	+	+	
Spinal	+	+	+	
Respiratory Function	↓			
GI Tract	↓ motility	↓ motility		
Psychotomimesis		↑		
Feeding	↑	↑	↑	
Sedation	↑	↑		
Diuresis		↑		
Hormones				
Growth Hormone	↑ release		↑	
Prolactin	↑ release			
Neurotransmitter Release				
Acetylcholine	Inhibit			
Dopamine			Inhibit	
Endogenous ligand	β-Endorphin, Endomorphin	Leu-enkephalin, Met-enkephalin	Dynorphin	Nociceptin
Agonist	Morphine, Fentanyl	Deltorphin	Buprenorphine, Pentazocine,	—
Antagonist	Naloxone, Naltrexone	Naloxone, Naltrindole	Naloxone	—
Coupled G protein	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Adenylate cyclase	Inhibition	Inhibition	Inhibition	Inhibition
Voltage-gated Ca^{2+} channels	Inhibition	Inhibition	Inhibition	Inhibition
Inward rectifier K^+ channels	Activation	Activation	Activation	Activation

Analgesic effects of opioids arise from their ability to inhibit directly the ascending transmission of nociceptive information from the spinal cord dorsal horn and to activate pain control circuits that descend from the midbrain, through the rostral ventromedial medulla (RVM), to the spinal cord dorsal horn. Opioid receptors are also expressed in the amygdala, the mesencephalic reticular formation, the periaqueductal grey (PAG), and the RVM.

Analgesic actions are also mediated by a net inhibitory effect from the PAG and RVM on nociceptive processing in the spinal dorsal horn. Opioid receptors are abundantly expressed in the substantia gelatinosa, where glutamate and substance P release from the primary sensory neuron is inhibited by opioids. Histamine receptors are known to participate in spinal cord nociceptive transmission and have been shown to participate in opioid analgesic mechanisms.

Opioids may also produce analgesia through the peripheral mechanism. Immune cells infiltrating the inflammation site may release endogenous opioid-like substances, which act on the opioid receptors located on the primary sensory neuron.

Apart from the principal receptors μ, κ and δ, opioids also act by interacting with molecules other than opioid receptors. Opioids have also been shown to possess local anaesthetic properties, adrenoceptor agonist properties and activity at serotonin type 3A (5-HT_{3A}) receptor, which is / linked to gastrointestinal motility, visceral pain, nausea, and vomiting. Unlike morphine, fentanyl does not affect 5-HT_{3A} activity significantly.

N-methyl-D-aspartate (NMDA) glutamate receptors are important in the development of opioid tolerance and increased pain sensitivity. Prolonged exposure to opioids activates NMDA receptors via second messenger mechanisms and also downregulates spinal glutamate transporters. The resultant high synaptic concentrations of glutamate and NMDA receptor activation contribute to opioid tolerance and abnormal pain sensitivity (*Opioid Induced Hyperalgesia*).

Central Nervous System

- *Analgesia:* It reduces both the sensory and affective aspects of pain
- *Euphoria:* A pleasant floating sensation with lessened anxiety and distress is experienced. However, dysphoria, an unpleasant state characterized by restlessness and malaise, may also occur.
- *Sedation:* Drowsiness and clouding of mentation with little to no amnesia is produced. These effects are more marked in the elderly than the younger population.
- *Cerebral Metabolic rate and Cerebral Blood Flow:*
    - Modest decreases in cerebral metabolic rate are observed.
        - Neuroexcitation and focal seizure activity can cause regional increases in brain metabolism
    - Effect on blood flow depends on concomitant anaesthetics administered.
        - When vasodilation is produced by co-administered anaesthetics, opioids are more likely to cause cerebral vasoconstriction.
        - Decrease cerebral blood flow (CBF) when they are combined with nitrous oxide (N_2O).
        - When administered alone or when the co-administered anaesthetics cause cerebral vasoconstriction, there is usually no effect or a small increase in CBF.
        - CBF changes induced by fentanyl are regionally heterogenous
- *Intracranial Pressure (ICP):* Effects on ICP are minimal under conditions of controlled ventilation.
- *Sleep Architecture:* Although the mechanism by which opioids interact with circadian rhythm is unclear, they can decrease the percentage of stage 3 and 4 sleep, which may result in fatigue and other sleep disorders, including sleep-disordered breathing and central sleep apnoea.
- *Hallucinations*: Auditory, visual, or rarely, tactile hallucinations.

- *Muscle Rigidity*: Increased muscle tone which may progress to rigidity and severe stiffness in certain cases is also seen with fentanyl. The precise mechanisms are not known but experimental studies point towards activation of central μ-receptors, whereas supraspinal δ1 and κ1 receptors may attenuate this effect. Its development is affected by dose and rate of administration, use of nitrous oxide, concomitant muscle relaxants and age. It usually develops just as a patient loses consciousness and its effects include
    - Haemodynamic effects: Increase in central venous pressure, peak airway pressure and peripheral vascular resistance
    - Respiratory effects: ↓ Compliance, ↓ FRC, ↓ ventilation, ↑ O_2 consumption → Hypercarbia, Hypoxaemia
    - Raised intracranial pressure

  Certain features and neurochemical mechanisms of this muscle rigidity also resemble Parkinson's disease and caution needs to be exercised when administering fentanyl to such patients due to risk of dystonia.

  It is reversed by opioid antagonists like naloxone and muscle relaxants. It can be prevented and attenuated by using benzodiazepines in subanaesthetic doses, anaesthetic induction doses of thiopentone and concomitant use of muscle relaxants.
- *Pupillary Size:* most μ– and κ–agonists cause constriction of the pupil (miosis) by an excitatory action on the parasympathetic nerve innervating the pupil though stimulation of the Edinger–Westphal nucleus. Little or no tolerance develops to this, even in highly tolerant addicts making this useful for diagnosis of overdose.
- *Electroencephalogram (EEG):* β-activity is initially decreased, and α-activity is increased; subsequently α-activity disappears, and δ-activity predominates. Small doses of fentanyl (2-5 μg/kg) produce minimal EEG changes, whereas higher doses (30-70 μg/kg) result in high-voltage slow (δ) waves suggesting a state consistent with anaesthesia. Although transient isolated (usually frontotemporal) sharp wave activity can be observed after large doses of

fentanyl and other opioids, it is not generalized. No epileptic spike-wave patterns are demonstrable on the EEG

- *Nausea and vomiting*: The opioid analgesics can activate the brainstem chemoreceptor trigger zone to produce nausea and vomiting. As ambulation seems to increase the incidence of nausea and vomiting there may also be a vestibular component in this effect.
- *Temperature regulation:* Mediated in part by the action of endogenous opioid peptides in the brain. For example, administration of μ-opioid receptor agonists, such as morphine to the anterior hypothalamus produces hyperthermia, whereas administration of κ agonists induces hypothermia. Fentanyl has little effect on post-operative shivering
- *Pruritus:* Fentanyl may lead to flushing and warming of the skin associated with sweating, urticaria, and itching at times. Peripheral histamine release was thought to be the primary mechanism for long but it has been observed that all opioids can cause pruritus via a central (spinal cord and medullary) action on pruritoceptive neural circuits. Opioid anatagonists like naloxone have been found to be beneficial but their use for treatment of this pruritus is limited due to their antagonism of opioid induced analgesia as well.
- *Opioid Induced Hyperalgesia (OIH):* Spinal sensitisation to glutamate and substance P have been shown to be responsible for this effect. Abrupt withdrawal after prolonged administration also triggers OIH but mechanisms are not clear so far. Ketamine has been shown to offer some relief indicating a role of the NMDA receptor stimulation.

Respiratory System

- *Respiratory Depression:* Dose dependent respiratory depression is seen with fentanyl due to activation of the μ-receptors causing a direct action on the brainstem respiratory centres. There is decrease in hypoxic ventilatory drive and an increase in thresholds of apnoea and CO_2 levels which usually stimulate respiration. Higher doses, advanced age, concomitant

CNS depressants, decreased clearance and secondary peaks all increase the risk of respiratory depression after fentanyl administration

- *Effects on Airways:*
    - While most opioids cause central suppression of cough reflex, rapid injection of fentanyl may provoke cough. This may be prevented by slower rate of injection, preconditioning with a smaller dose of fentanyl, premedication with lignocaine, propofol, α_2 agonists, inhaled β_2 agonists and NMDA antagonists.
    - Prevent increases in bronchial muscular tone decreasing the possibility of bronchospasm especially in asthmatic patients. Antihistaminic, antimuscarinic and antiserotonergic actions of fentanyl add on to this effect
    - Physiological airway protection responses like mucous secretion and rapid movement of cilia may also be suppressed by fentanyl.

Cardiovascular System

- Key areas of the brainstem that integrate cardiovascular responses and maintain cardiovascular homeostasis are the nucleus solitarius, the dorsal vagal nucleus, the nucleus ambiguous, and the parabrachial nucleus.
- The most significant cardiovascular effect of fentanyl is bradycardia of vagal origin; cardiac output, mean arterial pressure, pulmonary and systemic vascular resistance, and pulmonary capillary wedge pressure are unaffected by the administration of the drug.
- *Hypotension:* Patients who are volume depleted, or individuals depending on high sympathetic tone or exogenous catecholamines to maintain cardiovascular function, are predisposed to hypotension after opioid administration. This is seen less frequently with fentanyl as it causes much less histamine release compared to other opioids.
- *Heart Rate:* Bradycardia may be seen due to loss of sympathetic tone and stimulation of vagal nuclei. Fentanyl may also depress cardiac conduction by direct membrane actions and

is known to predispose to prolongation of QT interval during cardio-pulmonary bypass. However, these effects are rare and predisposition to rhythm disturbances after fentanyl is mostly seen in patients already on calcium channel blockers and beta blockers.

- *Cardiac Contractility:* Fentanyl produces little or no change in myocardial contractility. Usually, most hemodynamic variables remain unchanged after large doses of fentanyl.
- Premedication with Fentanyl attenuates cardiovascular responses associated with tracheal intubation after induction of general anaesthesia.
- Clinically, high doses of opioids can maintain myocardial perfusion and the O_2 supply-demand ratio as well or better than can inhalation-based techniques.
- Coronary conductance is regulated by arterial baroreflex control, and vasodilator response is induced by a rise in aortic pressure. This baroreflex control is enhanced by low plasma concentration of fentanyl (1-2 ng/mL), but appears to be depressed at increased concentrations of fentanyl.
- Fentanyl is also known to enhance the oculo-cardiac reflex

Endocrine System

In humans, opioids generally increase growth hormone, thyroid stimulating hormone, and prolactin, and decrease luteinizing hormone, testosterone, oestradiol, and oxytocin. The effects of opioids on arginine vasopressin and ACTH are conflicting. The primary endocrine disorder that results from opioid misuse is hypogonadism, particularly in males. Fentanyl is more effective than morphine in modifying hormonal responses to surgery in a dose dependent manner. Although sympathetic and hormonal stress responses cannot be completely suppressed.

Gastrointestinal System

- Fentanyl decreases gastrointestinal motility and decreases gastric acid secretion. It also increases the common bile duct pressure by causing spasm of the sphincter of Oddi which may cause increased plasma amylase and lipase levels.
- Stimulation of the chemoreceptor trigger zone in the area postrema of the medulla possibly through δ-receptors, leads to nausea and vomiting.

Renal and Genito-Urinary System

- Renal function is depressed by opioids probably due to decreased renal plasma flow.
- While, μ opioids have an antidiuretic effect in humans, fentanyl does not cause an increase in anti-diuretic hormone like morphine
- Fentanyl increases the tone of the ureters, bladder detrusor muscle, and vesicular sphincter.

Obstetric Effects

- Fentanyl inhibits uterine contractility at supra-clinical concentrations. Prolongation of labour has been observed.
- Fentanyl readily crosses placenta but does not cause neonatal depression except when extremely large doses are administered and its teratogenic effects are minimal. Nevertheless, extreme caution must be exercised while using fentanyl in pregnant patients and its use should be restricted to first stage of labour or after the delivery of baby.
- Fentanyl is secreted in breast milk in a ratio of 2:1 to 3:1 with plasma but effects on the babies appear to be minimal

Miscellaneous Effects

- *Anaphylactoid Reactions:* Histamine release by fentanyl is minimal therefore allergic reactions are rare and are usually seen due to preservatives
- *Ocular Pressure:* Fentanyl is effective at preventing increase in ocular pressure in response to tracheal intubation.
- *Immune Effects:* Fentanyl has no effect on white cell function although intravenous injection causes a rapid increase in NK cell activity in peripheral blood. Effects on cancer progression are under study

Indications, Contraindications and Adverse Effects

Indications

- **Analgesia:** As part of general anaesthesia or regional anaesthesia technique. Fentanyl can produce potent short acting analgesia making it suitable for monitored anaesthesia care as well. It can also be used as intravenous or epidural infusions and as part of patient controlled anaesthesia regimens
- **Sedation:** Fentanyl can be and is used extensively in ICUs as part of treatment for pain anxiety and agitation. It is also used in mechanically ventilated patients as infusion to improve tube tolerance and compliance to mechanical ventilation.
- **Balanced Anaesthesia:** Addition of fentanyl to sedative-hypnotics like thiopentone or propofol along with volatile anaesthetics helps to attain anaesthetic conditions with stable haemodynamics, reduced pre-operative anxiety, decreased somatic and autonomic responses to airway manipulation, limited use of volatile agents and immediate post-operative analgesia. This usually requires a loading dose of fentanyl (2-6 μg/kg) with a sedative-hypnotic and a muscle relaxant. Maintenance of anaesthesia can be achieved with low concentrations of potent inhaled anaesthetics, and additional fentanyl (intermittent boluses of 25-50 μg every 15-30 minutes or a constant infusion of 0.5-5.0 μg/kg/h)

- **Total Intravenous Anaesthesia (TIVA)**
- **High Dose Opioid based anaesthesia for cardiac surgeries:** Fentanyl helps to maintain stable haemodynamic conditions throughout the induction-intubation period. High doses have also been proven to be safe and effective in paediatric age groups for this purpose. It is also not associated with post-operative cognitive dysfunction.

Contraindications

- Concomitant use with a partial opioid agonist such as petazocine or buprenorphine may diminish analgesic effects or produce a state of withdrawal
- It should be used cautiously in patients with head injuries as CO_2 retention caused by respiratory depression results in cerebral vasodilation. In patients with elevated intracranial pressure, this may lead to lethal alterations in brain function.
- In patients with borderline respiratory reserve, the depressant properties of the opioid analgesics may lead to acute respiratory failure.
- There may be prolonged action in patients with hepatic or renal insufficiency. Therefore it should be used cautiously in such patients
- Patients with adrenal insufficiency (Addison's disease) and those with hypothyroidism (myxoedema) may have prolonged and exaggerated responses to administration of fentanyl

Adverse Effects

- Respiratory depression
    - This effect may be exaggerated by amphetamines, phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants.
- Provocation of cough reflex
- Muscle rigidity leading to difficulty in ventilation due to decreased compliance of chest wall as well as laryngeal muscle contraction

- Gastro-intestinal smooth muscle spasm which may lead to constipation, biliary colic and delayed gastric emptying
- Nausea and vomiting
- Pruritus and urticaria
- Myoclonic activity and seizures
- Urinary retention
- Tolerance and dependence may develop with prolonged use. Tolerance develops to analgesic, euphoric, sedative, depression of ventilation, and emetic effects of opioids but not to their effects on miosis and bowel motility.
- Withdrawal reactions may be seen with sudden cessation after administration over a long period. Initial symptoms of withdrawal include yawning, diaphoresis, lacrimation, or coryza. Insomnia and restlessness are prominent. Abdominal cramps, nausea, vomiting, and diarrhoea reach their peak in 72 hours and then decline over the next 7 to 10 days.

ECHOCARDIOGRAPHY[45, 46]

Echocardiography (echo) is the use of ultrasound to examine the heart. It is a powerful, safe, non-invasive and painless technique for cardiovascular investigation and has become widely available. It is a practical procedure requiring skill and is operator dependent. Since its introduction in 1950s by Edler and Hertz it has become the second most common cardiovascular investigation requested after ECG.

ULTRASOUND

Sound is a disturbance propagating in a material which may be air, water, body tissue or a solid substance. It is a mechanical wave composed of compressions and rarefactions of molecules in the said medium. It is characterised by its frequency and intensity.

Frequency of sound is measured in Hertz (Hz) which is essentially the number of oscillations of the wave per second. The human ear can distinguish sounds between 20 Hz to 20000 Hz (20 kiloHertz, kHz). Sounds with frequencies higher than 20kHz cannot be perceived by humans and is termed *ultrasound*. The nature of the material in which sound propagates determines the velocity in that material. Wavelength of the sound wave is the ratio of its velocity to its frequency.

In ultrasonographic examination, the shorter the wavelength, the higher the resolution. At the same time, due to the shorter wavelength, penetration power of the wave is reduced. Therefore, a compromise needs to be reached between resolution and penetration in terms of wavelength and frequency. Higher frequencies are used in linear-array transducers to visualize superficial structures, most commonly vasculature, soft tissues, and joints. Lower frequencies are used in curvilinear and phased-array transducers to visualize deep structures in the thorax, abdomen, and pelvis.

Since sound is a form of energy, and we are transferring it to the body tissues, heat generation is also one pf the parameters to be considered. This is measured as the intensity of the sound beam and

defined as the concentration of power per unit area (W/cm^2). Although this is more of a concern during therapeutic applications of ultrasound as in lithotripsy.

Ultrasound is produced through special materials called *piezoelectric crystals*. These possess the property of being able to convert electrical oscillations into mechanical oscillations or sound and vice versa. The basic principle of any ultrasonographic examination hinges on this ability of these crystals as they act as generators as well as receivers of sound. When ultrasound propagates in a uniform medium, it maintains its initial direction. Absorption, scattering, transmission, refraction and reflection of the sound waves occurs at interfaces of two different parts of the media which have different densities. This acoustic impedance is utilised in ultrasonography as various tissues and their interfaces reflect, refract, absorb, transmit or scatter the sound differently. The reflected waves, received by the transducer are then converted into an electrical signal analysed by the machine to provide us an image. High reflection is white (e. g. bone), no reflection is black (air) and with differing intensities, different shades of grey are seen.

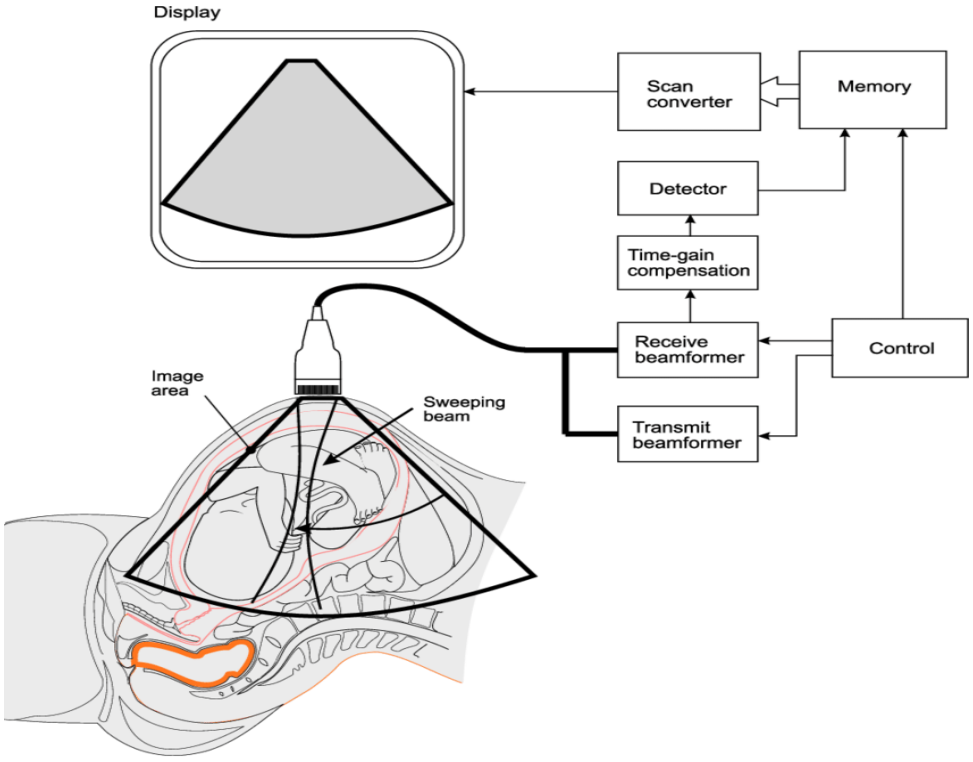


FIGURE 25: Principles of Ultrasonography

At its most basic, ultrasonography of any kind requires a transducer (which contains the piezoelectric components and transmits the beam), a convertor (the computer part of the machine which converts electric signals into images) and a screen to display the images.

Transducers typically contain 60 to 600 piezoelectric elements and are described by the arrangement of their elements as well as by their function and beam shape. There are four common types of transducers: linear, curvilinear, phased-array, and intracavitary as shown in the figure below

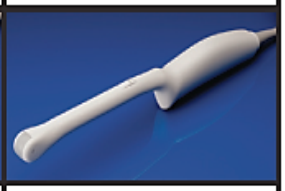
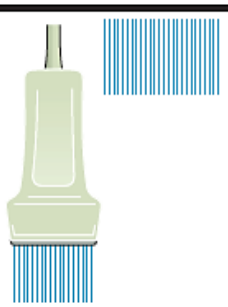
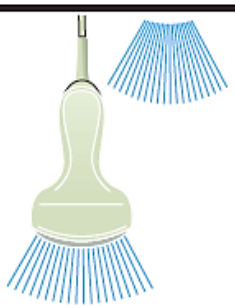
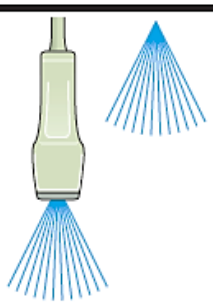
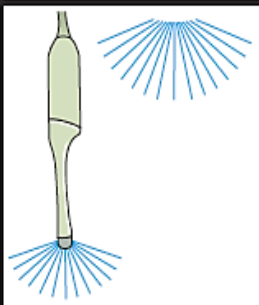
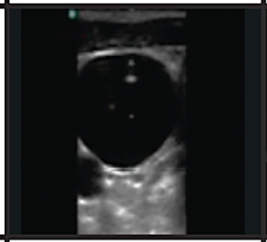
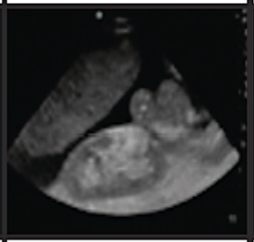
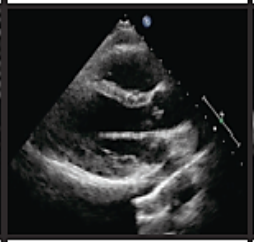
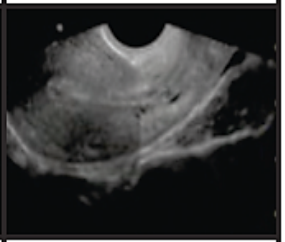
Transducer type	Linear	Curvilinear	Phased array	Intracavitary
				
Frequency range	5–15 MHz	2–5 MHz	1–5 MHz	5–8 MHz
Imaging depth	9 cm	30 cm	35 cm	13 cm
Footprint				
Image				
Applications	Arteries/veins Procedures Pleura Skin/soft tissues Musculoskeletal Testicles/hernia Eyes Thyroid Lymph Nodes Nerves	Gallbladder Liver Kidney Spleen Bladder Abdominal aorta Abdominal free fluid Uterus/ovaries Lumbar Puncture	Heart Inferior vena cava Lungs Pleura Abdomen Transcranial Doppler	Uterus/ovaries Pharynx

FIGURE 26: Ultrasonography Probe Types

ECHOCARDIOGRAPHY

The transducer or probe is placed on the anterior chest wall of the subject in trans-thoracic echo (TTE). In trans-oesophageal echo (TOE or TEE) a specialised probe is placed into the oesophagus with the beam directed towards the heart. The transducer used for TTE is the phased array transducer. Echo utilises ultrasound frequencies between 1.5 to 7.5 MHz. The velocity of sound in the heart is about 1540 m/s against 330 m/s in the air. Two quantities are measured in an echo

- Time delay between transmission of the pulse and reception of reflected echo.
- Intensity of the reflected signal.

Phased-array technology allows for more efficient two-dimensional imaging and is ideal for moving structures, such as the heart as

- Differential excitation of piezoelectric elements creates rapid electronic beam sweeping by sequentially pulsing multiple small crystals within the transducer.
- Steering and focusing of the ultrasound beam allows for a wider field of view than with linear transducers.
- The ability to steer ultrasound beams with phasing permits accurate velocity measurements when the vector of movement is not completely parallel with the beam. These unique characteristics make phased-array transducers ideal for cardiac and thoracic imaging.

Echo *Windows* and views

The TTE transducer usually has a dot or line to help place it in the correct position as well as for orientation of the image seen on the screen. There are many positions on the chest wall which facilitate good penetration by the ultrasound without too much masking and absorption by lungs or ribs. The heart is examined from these transducer positions in a number of sections. This needs to be done because

- Anatomy of heart and its surrounding structures limit the examination

- Standardised images are produced which can be compared between different studies

Technical difficulties are encountered in

- Very obese individuals
- Subjects with chest wall deformities
- Patients with chronic lung diseases

The main echo windows which are utilised to gain different views are given in the figure below

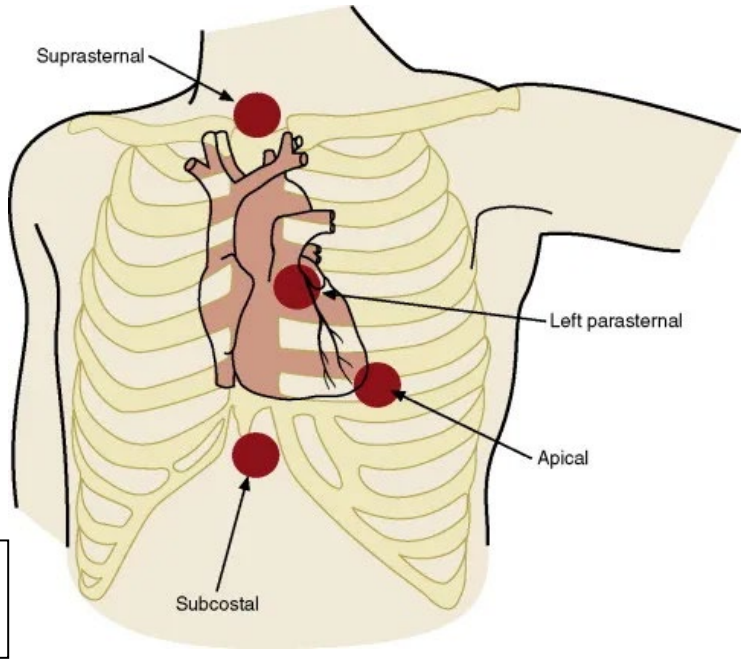


FIGURE 27:
Echocardiography Windows

Left Parasternal Window

- *Parasternal Long Axis view (PLAX):* Transducer is placed with the marker dot pointing towards right shoulder. Images of heart in long axis with slices from base of heart to apex are obtained

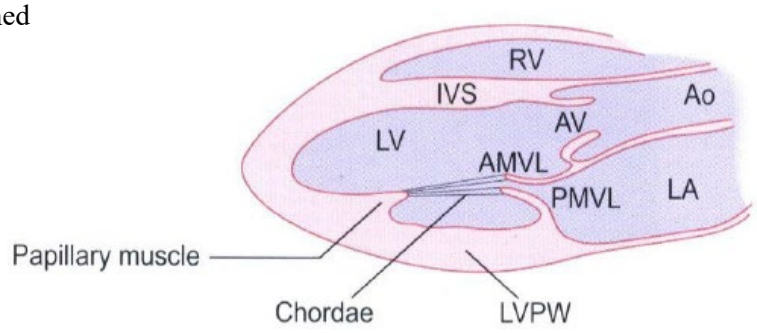
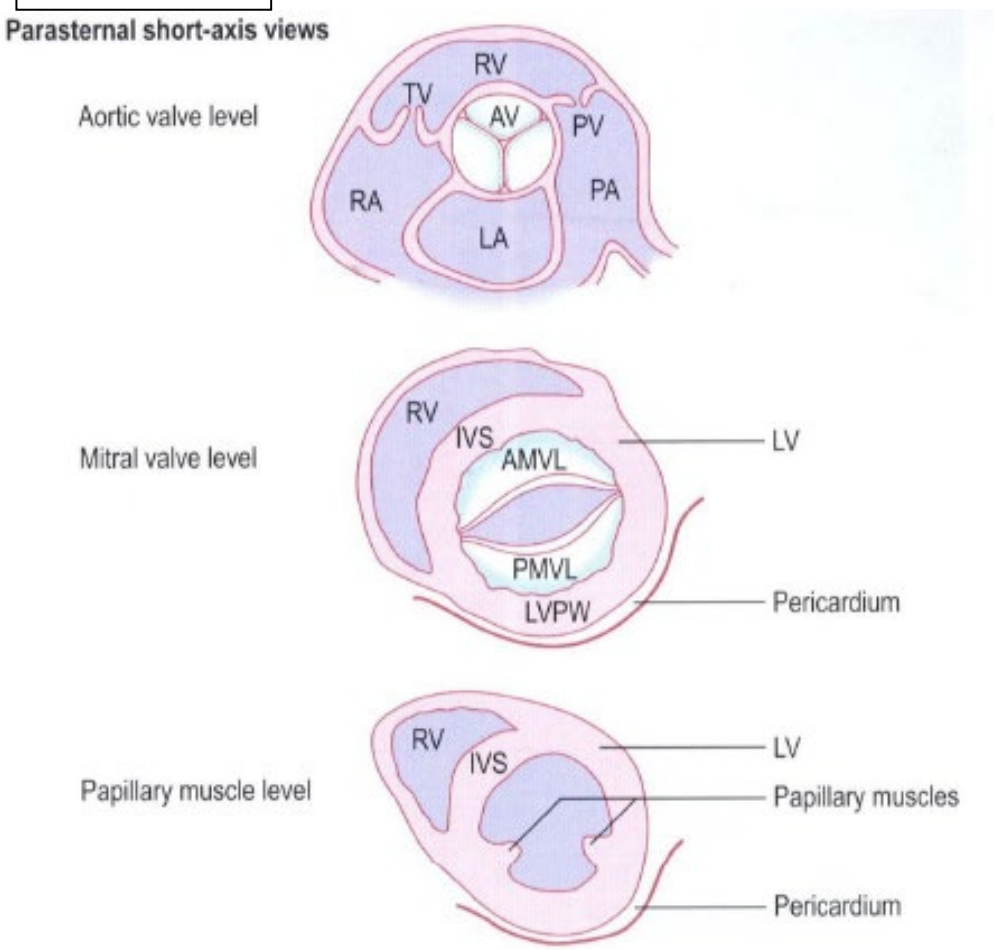


FIGURE 28: Left Parasternal Window

- *Parasternal Short Axis View:* In the same position as PLAX view, rotating the transducer by 90° such that the marker dot points to the left shoulder, we obtain the parasternal short axis (PSAX) view. By changing angulation of the transducer, four standard views are obtained
    - Level of Aortic Valve (AV)
    - Level of Mitral Valve (MV)
    - LV papillary muscles
    - LV Apex

FIGURE 29



Apical Window

- *4-Chamber View:* Probe is placed at apex of heart with marker dot pointing towards left shoulder

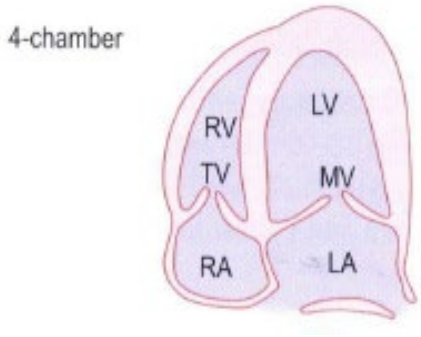


FIGURE 30

- *5-Chamber View (Including Aortic Outflow):* Angling the probe towards anterior chest wall in the same position as in 4-chamber view grants us this view. It is useful to assess aortic stenosis and regurgitation

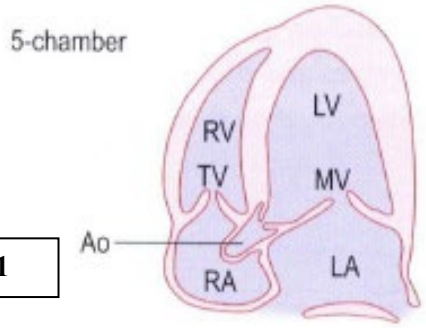


FIGURE 31

- *Long Axis and 2-Chamber Views:* Rotating the transducer at the apex provides us with these images which show different segments of left ventricle

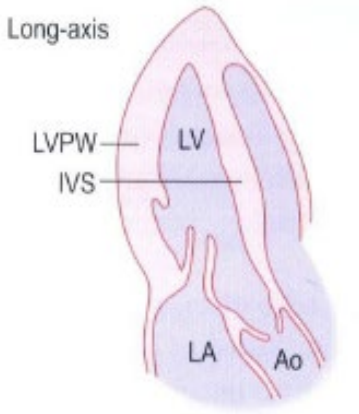


FIGURE 32

Subcostal View

It is similar to apical view but the probe is rotated by 90 degrees. It is useful in lung diseases, imaging interatrial septum, inferior vena cava (IVC) and abdominal aorta

Echocardiography Techniques

Three methods are used commonly. These modalities and their main uses are summarised in the table below

TABLE 4: Modalities if Echocardiography

2-D Echo		• Anatomy • Ventricular and Valvular movement • Positioning for M-Mode and Doppler
M-Mode		• Measurement of dimensions • Timing cardiac events
Doppler	**Pulsed Wave**	• Normal Valve Flow Patterns • LV Diastolic Dysfunction • Stroke Volume • Cardiac Output
	Continuous Wave	• Severity of Valvular Stenosis • Severity of Valvular Regurgitation • Velocity of flow in shunts
	Colour Flow Mapping	• Assessment of regurgitation and shunts

Assessment of LV Systolic Function

It can be assessed by all the three techniques described above.

- ***M-Mode:*** It is used to assess LV cavity dimensions, wall motion and thickness.
    - LVESD and LVEDD are measured at the level of MV leaflet tips in the PLAX view.
    - Measurements are taken from endocardium of left surface of interventricular septum to endocardium of left posterior wall
    - Ultrasound beam should be as perpendicular as possible to the interventricular septum
    - LV systolic function is estimated by calculating the following values through measurements obtained
        - *LV Fractional Shortening*: The percent change in LV internal dimensions between systole and diastole. Normal range is 30-45%

$$FS = \left(\frac{LVEDD - LVESD}{LVEDD}\right) \times 100\%$$

        - *LV Ejection Fraction*: It is the percent change in LV volume between systole and diastole. Normal range is 50-85%

$$FS = \left[\frac{(LVEDD)^3 - (LVESD)^3}{(LVEDD)^3}\right] \times 100\%$$

        - *LV wall motion*: Amplitude of the motion of IVS towards the posterior wall can be measured and used as an indicator of LV function
        - *LV Wall Thickness*: LV walls thicken during systole. Normal range of thickness at end-diastole is 6-10 mm. Thinning, stretching and scarring of the walls can be evaluated and various pathologies diagnosed and prognosed through this.

- ***2-D Echo:***
    - It can be used qualitatively to assess LV chamber in different planes and views
    - It is also useful for assessment of LV volumes and ejection fraction.
        - *Simpson's Method:* It is perhaps the most commonly used method for estimation of LV systolic function. The endocardial border is traced in systole and diastole. The cavity is divided into multiple slices of known thickness at different levels on short axis along the long axis. The volume of each slice is then measured. The thinner the slices, the more accurate is the measurement.

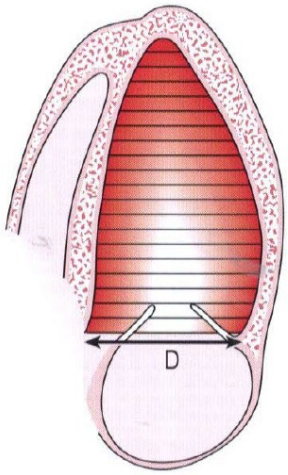


FIGURE 33: Simpson's Method for Estimation of Ejection Fraction

- Cardiac output can be estimated by using the obtained LV volumes

$$Cardiac\ output = Stroke\ Volume\ \times Heart\ Rate$$

$$Stroke\ Volume = LV\ End\ diastolic\ volume - LV\ end\ systolic\ volume$$

MATERIALS AND METHODS

Type of study: Randomised Clinical Trial

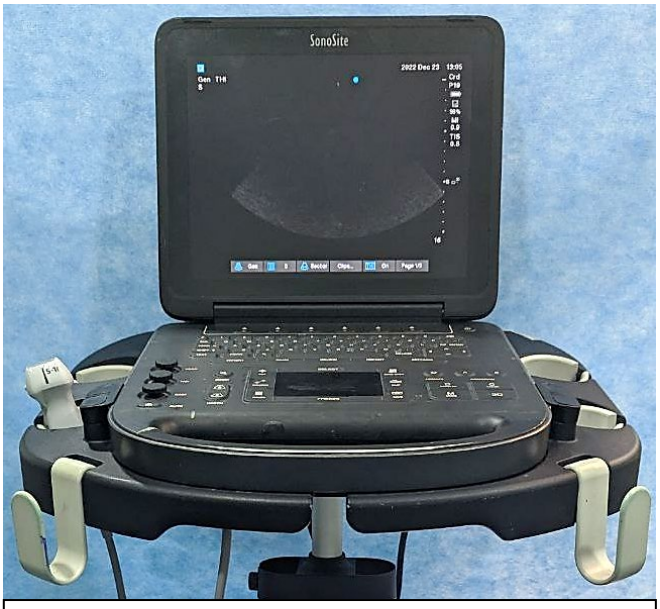
Duration of study and study population:

Adult patients posted for surgery under general anaesthesia between January 2021-December 2021 at KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehru Nagar, Belagavi-590010 were recruited as per inclusion and exclusion criteria.

Data Collection-12 Months

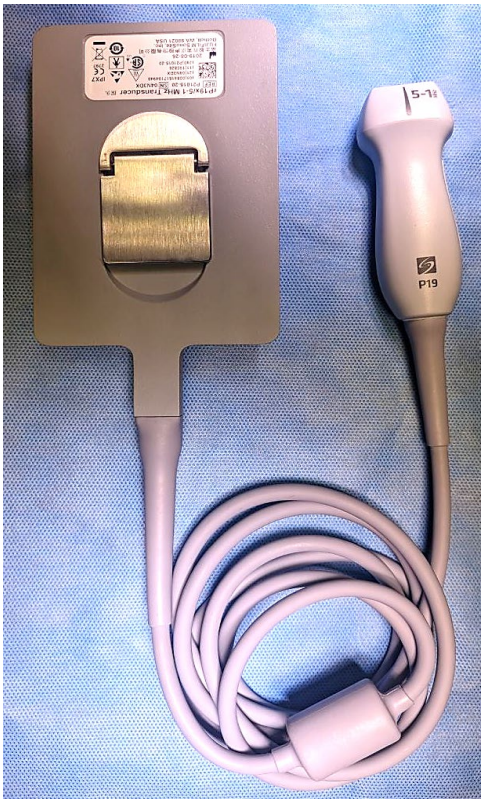
Equipment Used:

- Sonosite Edge II Total USG machine (Annexure 4 – Photograph 1)
- P19 5-1 MHz phased array probe (Annexure 4 – Photograph 2)



PHOTOGRAPH 1:

Sonosite Edge II Total USG Machine



PHOTOGRAPH 2:

P19 5-1 MHz Phased Array Probe

Patient Selection

Inclusion Criteria

- American Society of Anaesthesiologists physical status I and II.
- Age between 18 to 60 years.
- Patients undergoing elective surgeries under general anaesthesia.
- Provides Consent

Exclusion Criteria

- Patient undergoing emergency surgery.
- Patient who are unable or unwilling to give consent.
- Patients who do not fulfil inclusion criteria.
- Pre-existing cardiac diseases (Ischaemic Heart Disease, valvular and congenital heart diseases)

Sample Size Calculation

For a formula-based sample size, numerical values are required. Such values are generally available in medical literature. There is a dearth of studies of the nature that we are aiming for. Hence, there is no chance to get suitable numerical values.

As an alternative a sample size of 60 (30 in each group) is intended. In statistics, a sample size of ≥ 30 is considered a large sample. Generally, a large sample gives reliable outcomes.

Approval for conducting the study was obtained from the Departmental research committee and the clearance from the institutional ethical board. Written informed consent was obtained before enrolling healthy volunteers who are aged between 18 and 60 years belonging to ASA I and II category, in the study. After obtaining the approval of ethical committee and written informed consent, a total of 60 patients undergoing surgery under general anaesthesia were included in the study.

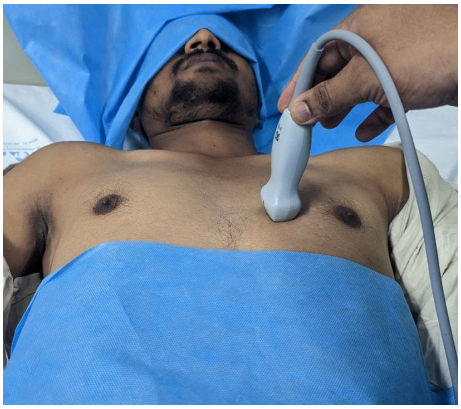
Patients were randomised based on computer generated randomization table into one of the following two groups.

Group P: Patients who were administered Propofol-Fentanyl for induction of GA.

Group T: Patients who were administered Thiopentone-Fentanyl for induction of GA.

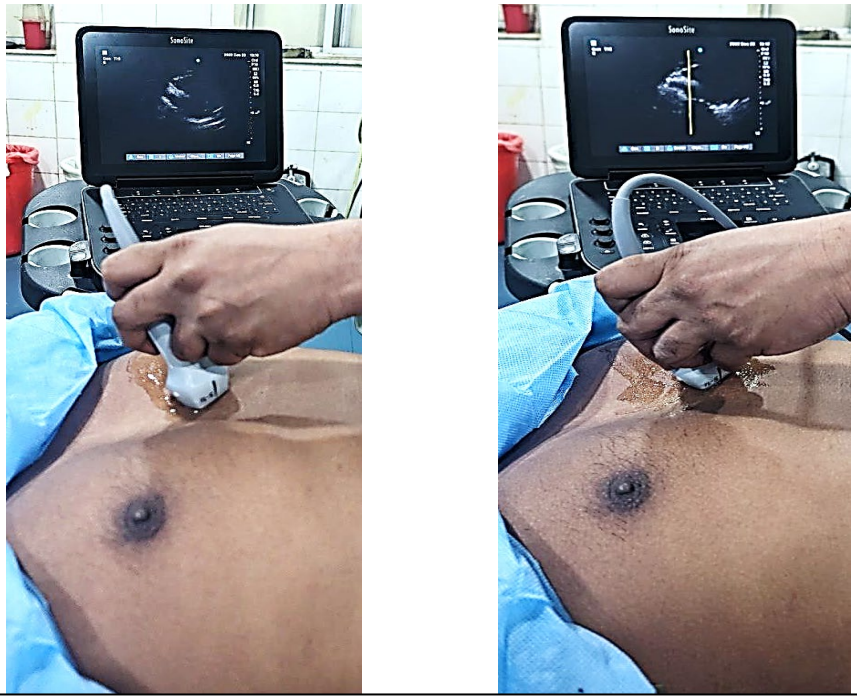
A thorough pre-anaesthetic evaluation was done on the day before surgery making note of any pre-existing medical co-morbidities. On the day of surgery, after assessing the patient and ensuring prescribed nil-by-mouth status, patients were placed in supine position (mimicking the position used during induction of general anaesthesia eventually) in the pre-operative holding area. Trans-thoracic echocardiography (TTE) was performed using Sonosite Edge II Total USG machine fitted with P19 5-1 MHz echocardiography probe. Examination was performed by myself and my guide Dr. Manjunath Patil who is trained in Point-of-Care Echocardiography under the guidance of my co-guide Dr. Prasad M.R.

The probe was placed in the left parasternal region between the 2nd and 4th intercostal space. The marker of the probe was then turned towards the right shoulder of the patient to obtain the *parasternal long axis (PLAX)* view (Annexure 4 – Photograph 3A).



PHOTOGRAPH 3: Probe Position for Parasternal Long Axis View

The right ventricle, left ventricle, aortic valve leaflets and mitral valve leaflets were identified. Subjects were asked to expire fully and hold their breath in order to minimise the effects of raised intrathoracic pressure and distortion of image produced by a full lung (Annexure 4- Photograph 4).

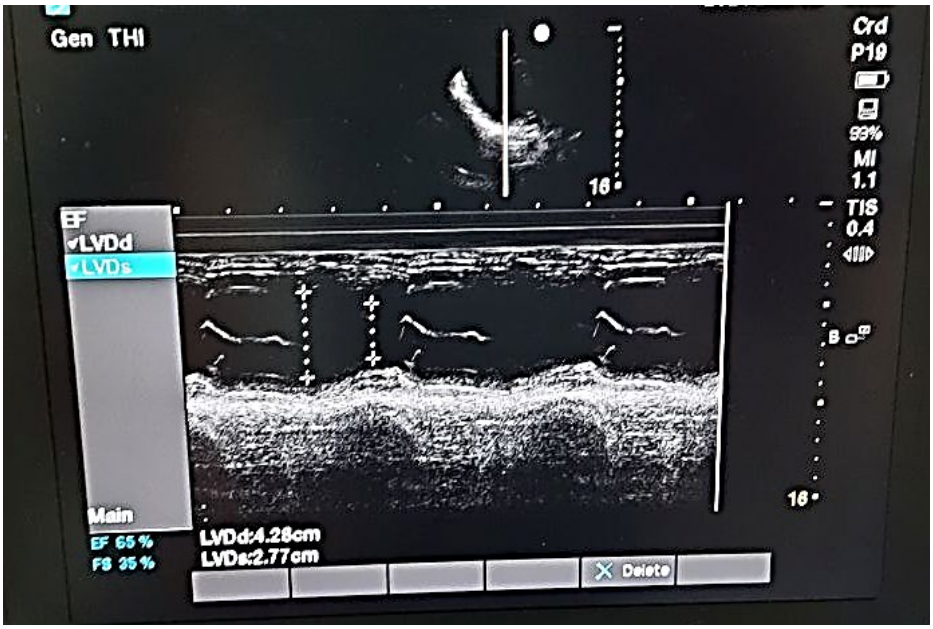


PHOTOGRAPH 4: Probe Position and Parasternal Long Axis View

Using M-mode, cross-sectional image of LV was obtained at a level just below the free edge of the anterior mitral leaflet.

Following parameters were measured as a baseline

- LV End Diastolic Diameter
- LV End Systolic Diameter
- LV Fractional Shortening
- LV Ejection Fraction using Simpson's method



PHOTOGRAPH 5: M-Mode Echocardiography and calculation of Fractional Shortening and Ejection Fraction

Intravenous access was secured using 18G or 20 G IV cannula and IV fluids started.

Patient were then shifted inside the operating room and standard monitoring devices were attached including non-invasive arterial blood pressure, heart rate, ECG and oxygen saturation.

Patients were then pre-oxygenated for three minutes. After this patient were administered Inj. Glycopyrrolate 0.004mg/kg, Inj. Midazolam 0.05mg/kg and Inj. Fentanyl 2 mcg/kg followed by the following

Group P: Inj. Propofol 2mg/kg IV

Group T: Inj. Thiopentone 5mg/kg IV

Muscle relaxation was achieved with the use of Inj. Vecuronium 0.1-0.2 mg/kg IV

Vital parameters including heart rate, blood pressure and oxygen saturation were measured at 0, 3- and 5-minutes post induction with above regimens. This data was collected as per the following table

TABLE 5: Vital Parameters Record

	BEFORE INDUCTION	AFTER INDUCTION		
		0 MIN	3 MIN	5 MIN
HEART RATE				
SYSTOLIC BLOOD PRESSURE				
DIASTOLIC BLOOD PRESSURE				
MEAN BLOOD PRESSRE				
OXYGEN SATURATION				

Patients were then intubated and placement of endo-tracheal tube confirmed with $EtCO_2$. After confirming tube placement and bilateral equal air entry, endotracheal tube was fixed.

Trans-Thoracic Echocardiography was then performed three minutes after the time of administration of induction agent using the same equipment and technique as earlier and the same parameters measured. Expiration hold was ensured in subjects by disconnecting them from the ventilator thereby negating the effects of positive pressure ventilation on the heart and improving the image by minimising the air in the lungs. Echocardiographic data was recorded in the following table

TABLE 6: Echocardiography Data Record

	BEFORE INDUCTION	AFTER INDUCTION	
		0 MIN	3 MIN
LV END DIASTOLIC DIAMETER			
LV END SYSTOLIC DIAMETER			
LV FRACTIONAL SHORTENING			
LV EJECTION FRACTION			

Complications were noted and recorded as following

TABLE 7: Complications Record

COMPLICATION	OBSERVATION
Desaturation	
Hypotension	
Arrhythmia	
Allergic Reactions	

All the examinations were performed by the same person so as to eliminate inter-observer bias.

Following this, anaesthetic management for rest of the surgery was continued as per standard institutional practice. At the end of the surgery, patients were reversed with Inj. Glycopyrrolate 0.008 mg/kg and Inj. Neostigmine 0.05 mg/kg after thorough oral suctioning and extubated

STATISTICAL ANALYSIS:

Statistical analysis was performed using *SPSS software Version 21*. As the study is focused on comparison of two groups. For the continuous quantitative variables mean and standard deviation has been calculated. The inter group continuous variables have been compared using suitable tools of statistics like unpaired student's t test. Two quantitative variables, within a group, have been compared using student's paired t test.

Discrete variables have been represented by median and nonparametric tests have been used for the same.

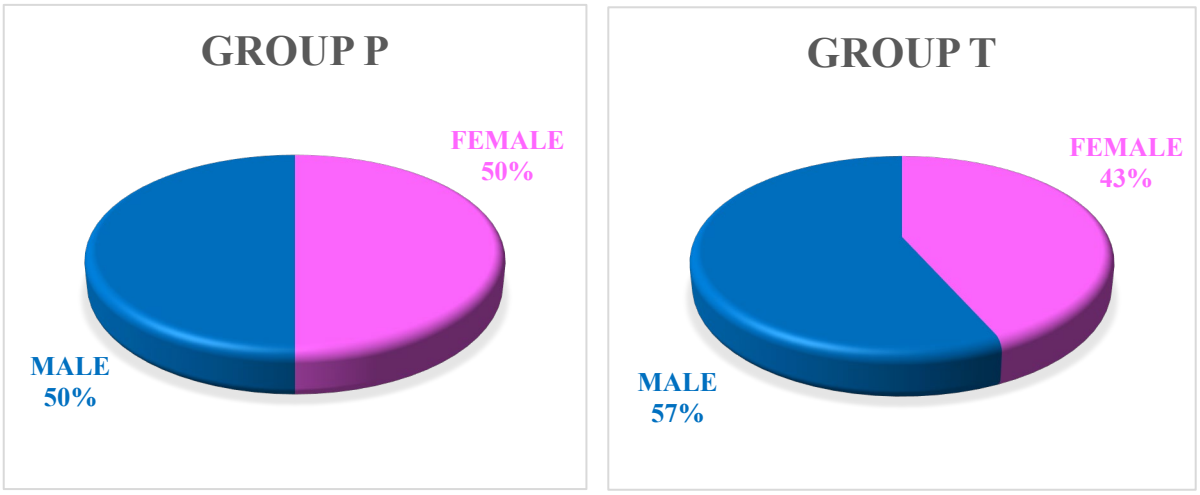
The association between the outcome, clinical and demographic characteristics have been tested using Chi-Square test.

For all the tests the value of p less than 5% (0.05) has been considered significant.

RESULTS

TABLE 8: Gender Distribution of Volunteers Studied

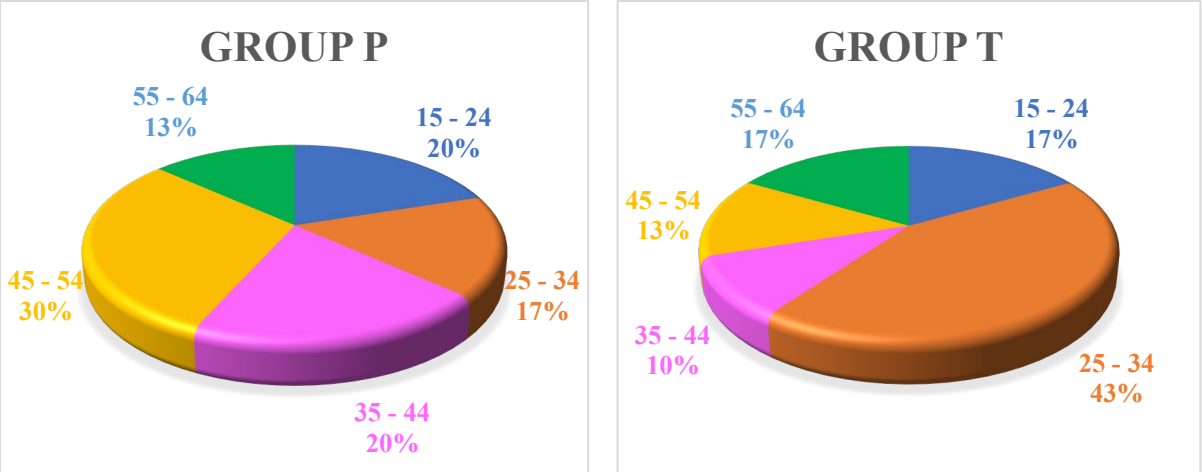
	GROUP P		GROUP T	
GENDER	**NUMBER**	**%**	**NUMBER**	**%**
FEMALE	15	50.00	13	43.33
MALE	15	50.00	17	56.67
TOTAL	30	100.00	30	100.00



GRAPH 9: Gender Distribution of volunteers in the two groups

TABLE 9: Age Distribution of Volunteers Studied

	GROUP P		GROUP T	
AGE (years)	**NUMBER**	**%**	**NUMBER**	**%**
15 - 24	6	20.00	5	16.67
25 - 34	5	16.67	13	43.33
35 - 44	6	20.00	3	10.00
45 - 54	9	30.00	4	13.33
55 - 64	4	13.33	5	16.67
TOTAL	30	100.00	30	100.00



GRAPH 10: Age Distribution of volunteers in the two groups

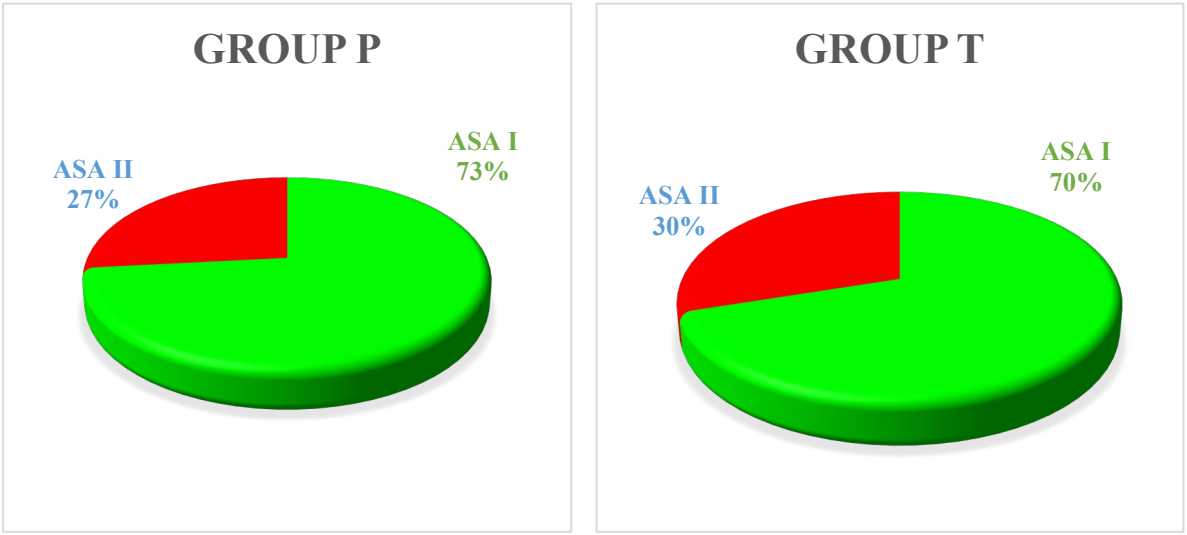
TABLE 10: Comparison of age distribution among two groups

	GROUP P				GROUP T			
	MIN	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**
AGE (years)	18	60	38.87	14.09	19	60	36.70	13.79

p-Value was found to be 0.55 on applying Student's unpaired t test, no significant difference was found in the age distribution among the two groups.

TABLE 11: American Society of Anaesthesiologist Grade Distribution of Volunteers Studied

	GROUP P		GROUP T	
ASA GRADE	**NUMBER**	**%**	**NUMBER**	**%**
I	22	73.33	21	70.00
II	8	26.67	9	30.00
TOTAL	30	100.00	30	100.00



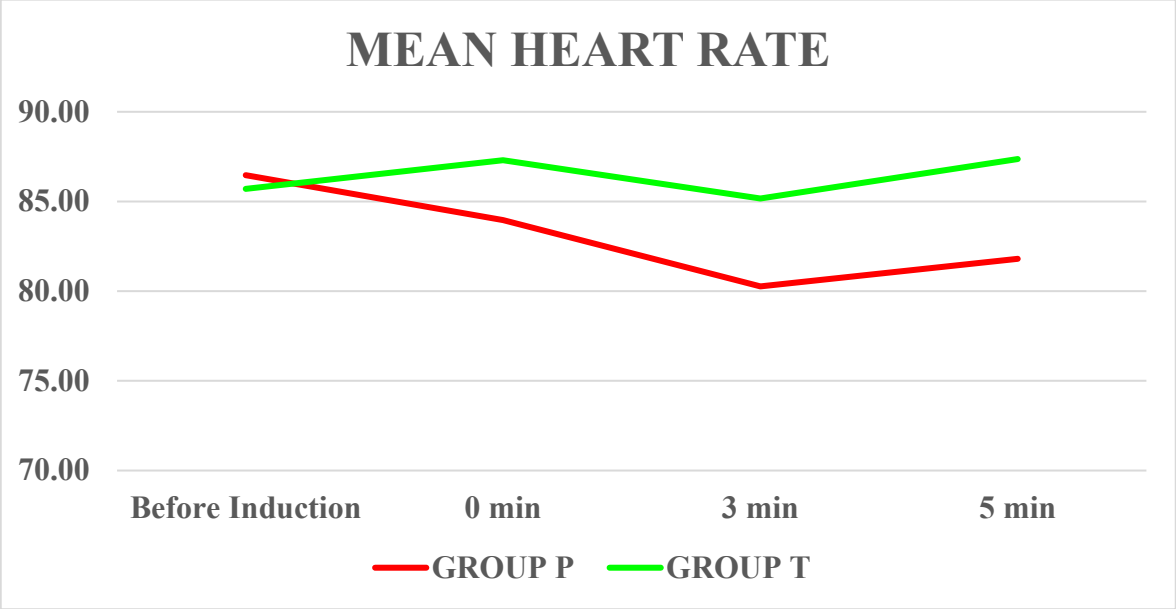
GRAPH 11: ASA Distribution of volunteers in the two groups

TABLE 12: Comparison of Effect on Heart Rate between the two groups

HEART RATE (bpm)		GROUP P				GROUP T			
		MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.
Before Induction		59	118	86.47	13.71	49	120	85.70	18.31
After Induction	0 min	67	106	83.97	10.41	53	122	87.30	19.33
	3 min	65	115	80.27	11.39	48	118	85.17	16.23
	5 min	64	115	81.80	13.54	57	140	87.37	17.64

S.D. – Standard Deviation; MIN- Minimum; MAX- Maximum

On applying Student's unpaired t-test on heart rates recorded prior to induction, p-value was found to be 0.85 implying no significant difference between the two groups. No significant difference was identified on applying the test on mean heart rates at 0, 3 and 5 minutes after induction with p-values of 0.40, 0.18 and 0.17 respectively. Comparison between mean heart rates of the groups is graphically presented below.



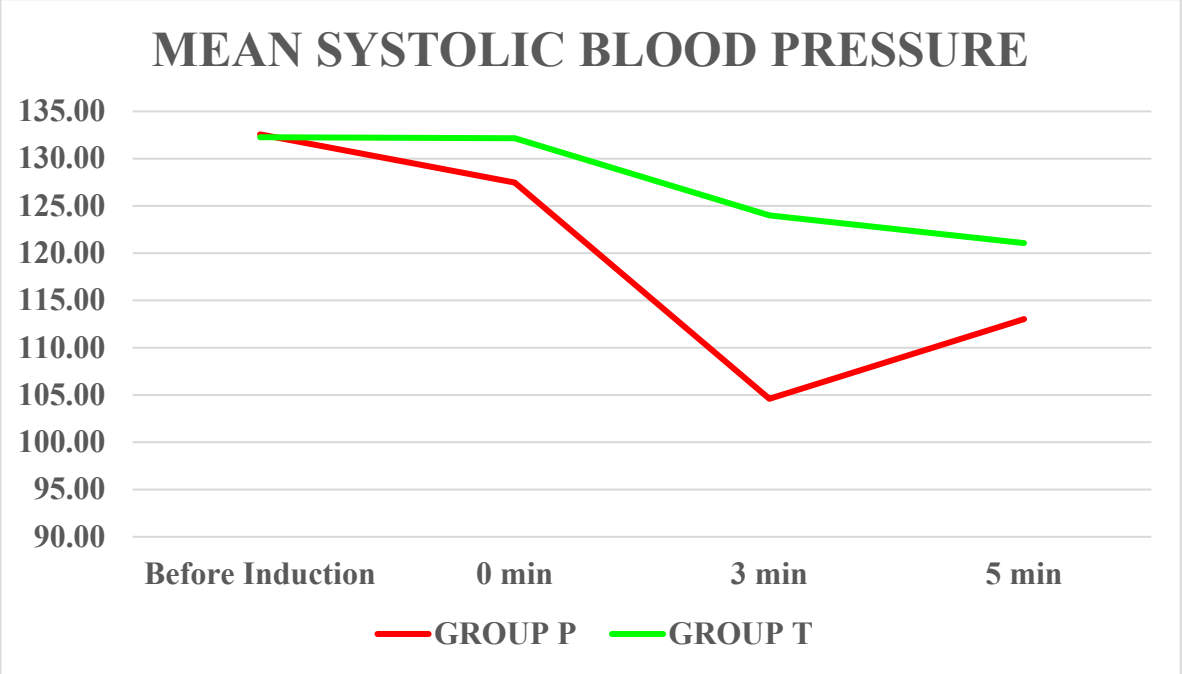
GRAPH 12: Effect on Heart Rate between two groups

TABLE 13: Comparison of Effect on Systolic Blood Pressure between the two groups

SYSTOLIC BLOOD PRESSURE (mmHg)		GROUP P				GROUP T			
		MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.
Before Induction		104	167	132.57	16.07	95	185	132.27	20.04
After Induction	0 min	101	159	127.47	14.80	94	191	132.17	21.48
	3 min	63	132	104.60	14.45	91	187	124.00	19.95
	5 min	90	137	113.03	12.30	97	159	121.07	15.60

S.D. – Standard Deviation; MIN- Minimum; MAX- Maximum

The effect of the two drugs as not found to be significant on systolic blood pressures prior to and at the time of induction with p-values of 0.95 and 0.33 respectively. At the 3-minute mark, a statistically significant difference was observed in Group P as compared to Group T pertaining to fall in SBP with a p-value of 0.0001. While some degree of recovery of SBP was observed 5 minutes after induction it was still lower in Group P and the difference between the groups was statistically significant (p-value 0.0307).



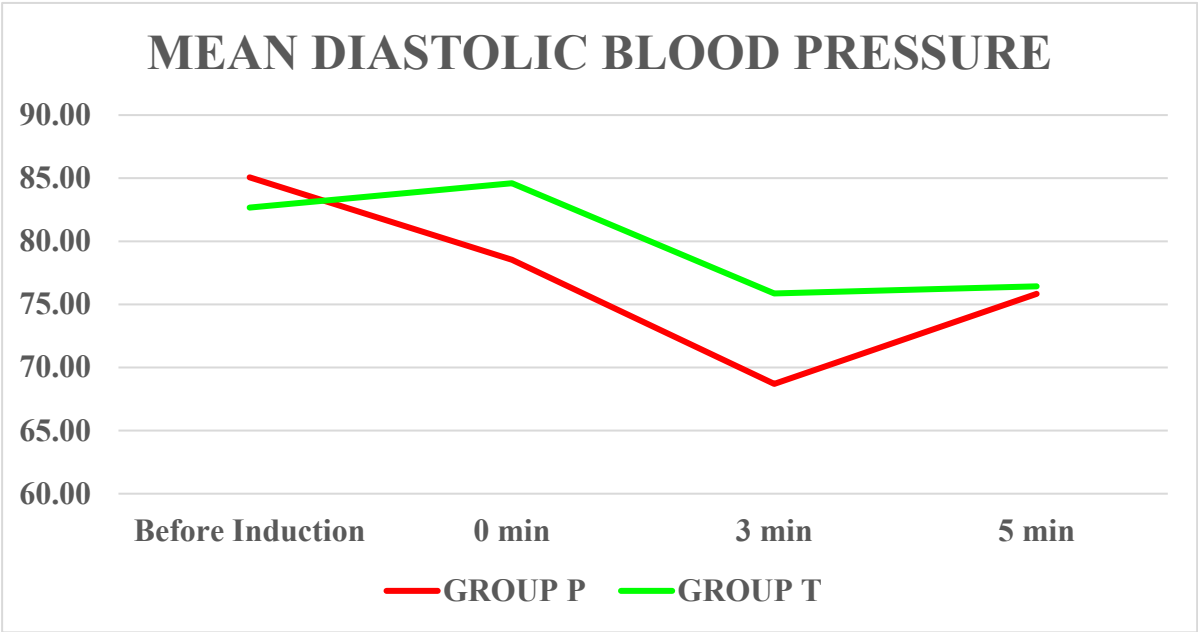
GRAPH 13: Effect on Mean Systolic Blood Pressure

TABLE 14: Comparison of Effect on Diastolic Blood Pressure between the two groups

DIASTOLIC BLOOD PRESSURE (mmHg)		GROUP P				GROUP T			
		MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.
Before Induction		58	138	85.07	14.95	52	112	82.67	16.17
After Induction	0 min	53	99	78.53	11.57	51	162	84.60	21.40
	3 min	43	90	68.70	11.13	46	104	75.87	14.27
	5 min	58	103	75.83	11.78	55	101	76.43	11.60

S.D. – Standard Deviation; MIN- Minimum; MAX- Maximum

As with systolic blood pressure, no significant difference was found between the two groups with respect to diastolic blood pressure before and at induction. The p-value on applying Student's unpaired t-test were 0.55 and 0.18 respectively. A fall is seen 3 minutes after induction which is greater in Group P. This difference is statistically significant with a p-value of 0.034. At the 5-minute mark, the diastolic blood pressures in Group P rise to match the values in Group T. However, with a p-value of 0.84, this is not found to be statistically significant.



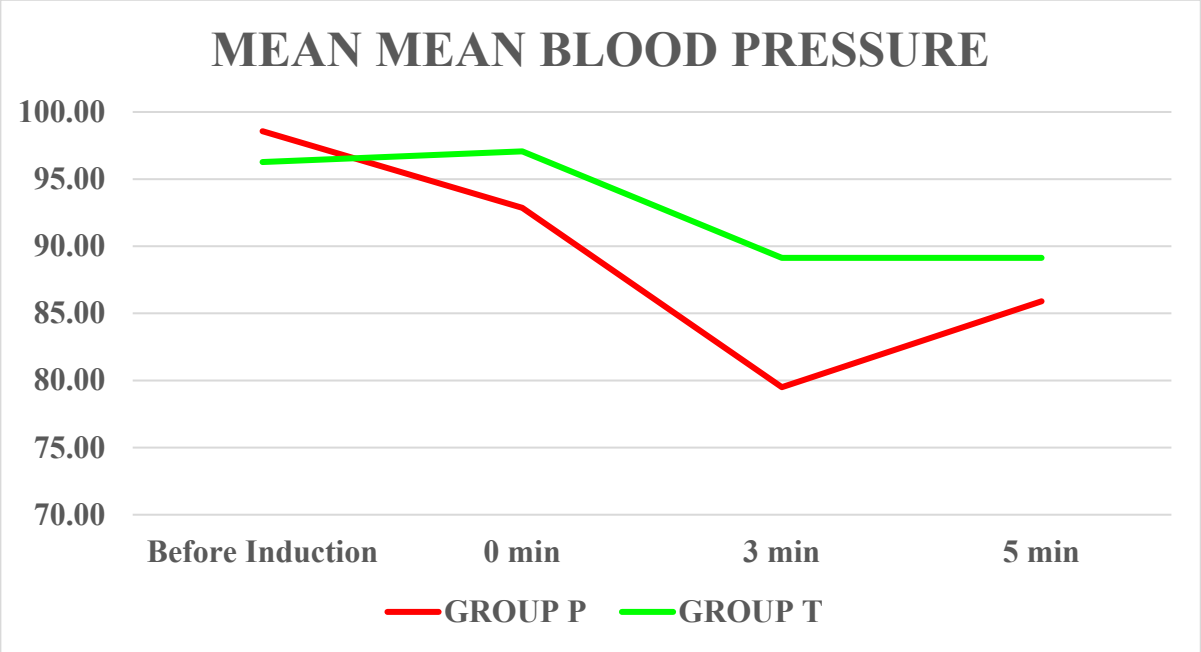
GRAPH 14: Effect on Mean Diastolic Blood Pressure

TABLE 15: Comparison of Effect on Mean Blood Pressure between the two groups

MEAN BLOOD PRESSURE (mmHg)		GROUP P				GROUP T			
		MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.
Before Induction		73	144	98.57	14.60	64	135	96.27	16.28
After Induction	0 min	69	111	92.87	11.78	61	170	97.07	21.90
	3 min	48	102	79.50	11.96	57	118	89.13	14.82
	5 min	66	112	85.90	12.81	65	113	89.13	12.24

S.D. – Standard Deviation; MIN- Minimum; MAX- Maximum

A similar pattern is seen when comparing the mean blood pressures among the two groups. A fall is seen at the 3-minute mark which is found to be statistically significant with a p-value of 0.007. Comparison at other times does not reveal a statistically significant relationship. P-values are found to be 0.57, 0.36 and 0.32 for mean blood pressure before induction, at induction and 5 minutes after induction respectively.



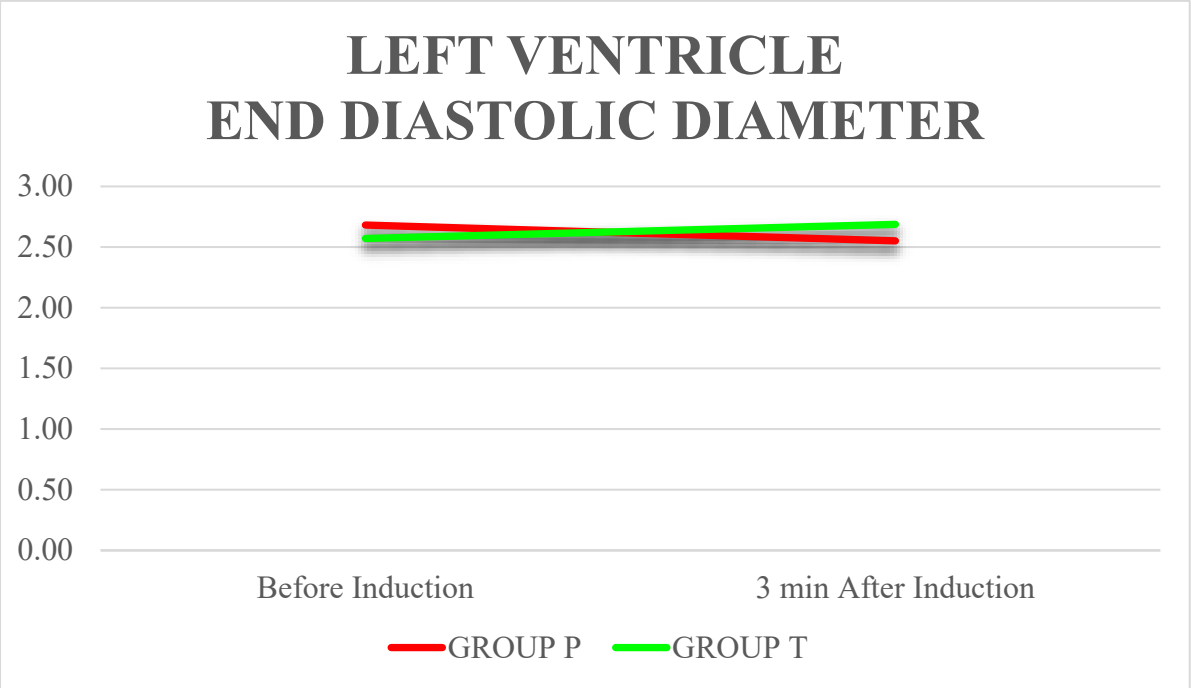
GRAPH 15: Effect on Mean Blood Pressure

TABLE 16: Comparison of Effect on Left Ventricle End Diastolic Diameter between the two groups

LVEDD (cm)	GROUP P				GROUP T			
	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.
Before Induction	1.26	4.94	2.68	0.98	1.07	4.18	2.57	0.78
After Induction 3 min	0.88	5.33	2.55	0.90	1.23	4.35	2.69	0.82

LVEDD-Left Ventricle End Diastolic Diameter; S.D. – Standard Deviation; MIN- Minimum; MAX- Maximum

Applying Student's unpaired t-test on measurements of left ventricular end diastolic diameter (LVEDD), p values obtained are 0.63 for diameters measured before induction and 0.54 for those measured three minutes after induction. Thus, the differences are not statistically significant.



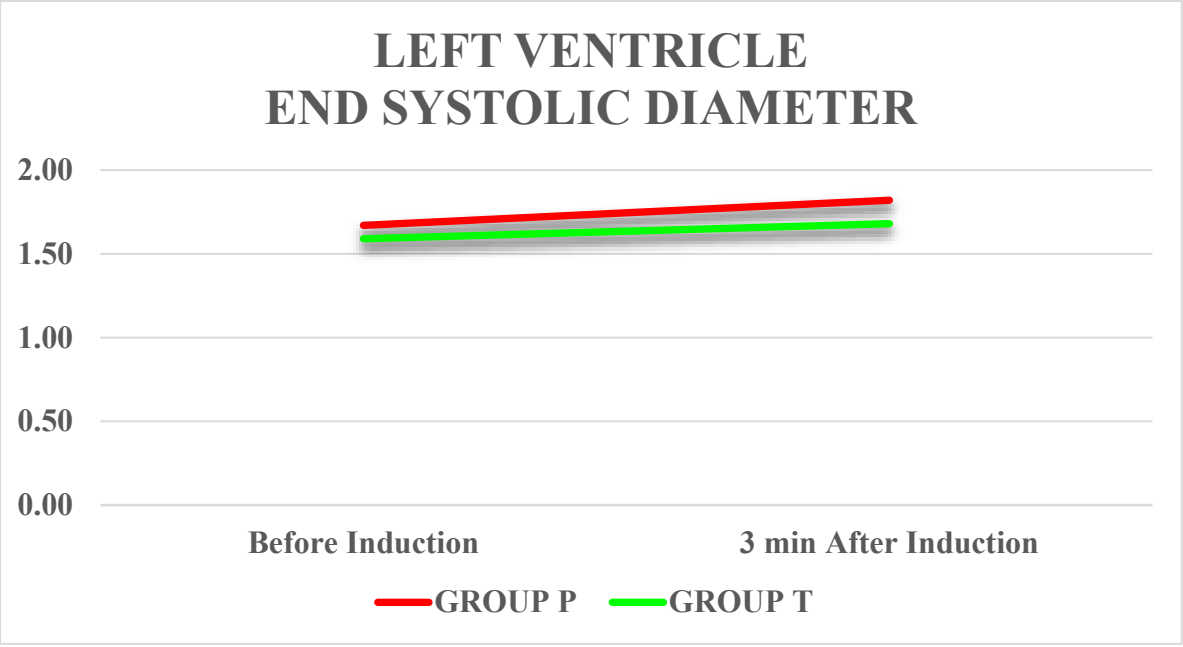
GRAPH 16: Effect on Left Ventricular End Diastolic Diameter

TABLE 17: Comparison of Effect on Left Ventricle End Systolic Diameter between the two groups

LVESD (cm)	GROUP P				GROUP T			
	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.
Before Induction	0.82	3.62	1.67	0.75	0.5	2.88	1.59	0.59
After Induction 3 min	0.63	3.92	1.82	0.72	0.74	2.96	1.68	0.61

LVESD-Left Ventricle End Systolic Diameter; S.D. – Standard Deviation; MIN- Minimum; MAX- Maximum

No statistically significant difference is found on comparison of left ventricle end systolic diameter (LVESD) between the two groups. The p-value for LVESD before induction is found to be 0.62 and that for 3 minutes after induction is 0.414.



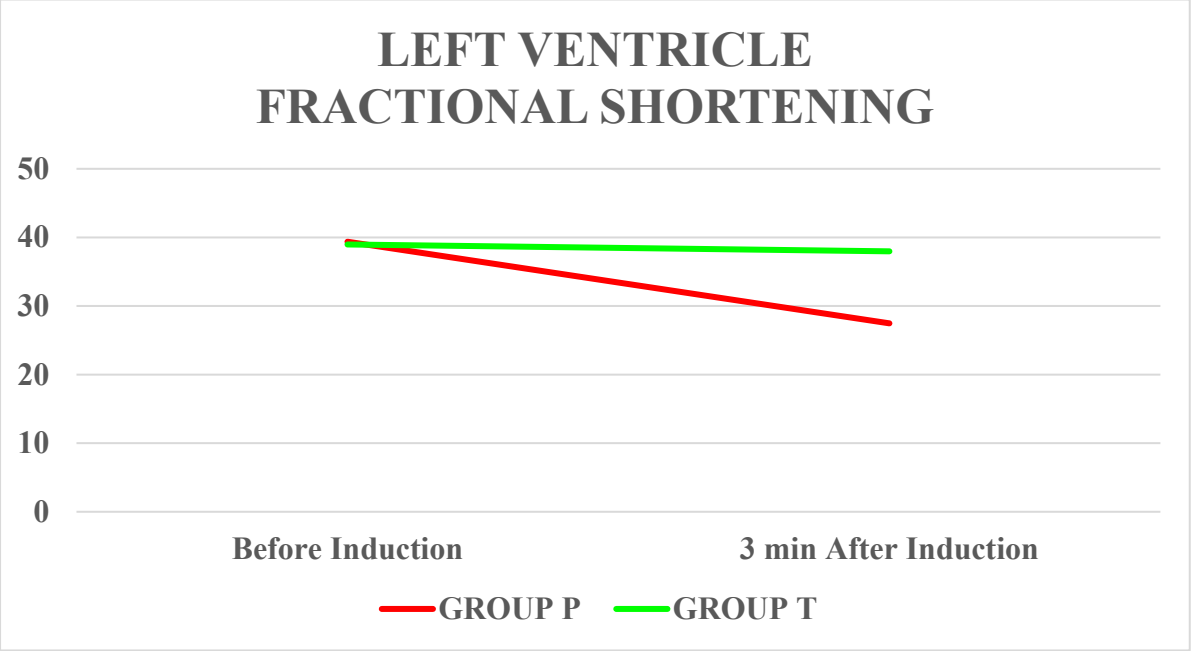
GRAPH 17: Effect on Left Ventricular End Systolic Diameter

TABLE 18: Comparison of Effect on Left Ventricle Fractional Shortening between the two groups

LVFS (%)	GROUP P				GROUP T			
	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.
Before Induction	27	58	39.37	9.52	25	59	38.97	8.60
After Induction 3 min	10	53	27.47	8.46	25	55	37.97	7.39

LVFS - Left Ventricle Fractional Shortening; S.D. – Standard Deviation; MIN- Minimum; MAX- Maximum

The comparison of left ventricular fractional shortening before induction of general anaesthesia among subjects does not reveal any statistically significant difference (p-value 0.86). On the other hand, comparison of this parameter as measured 3 minutes after induction reveals a statistically significant fall in Group P (p-value <0.0001).



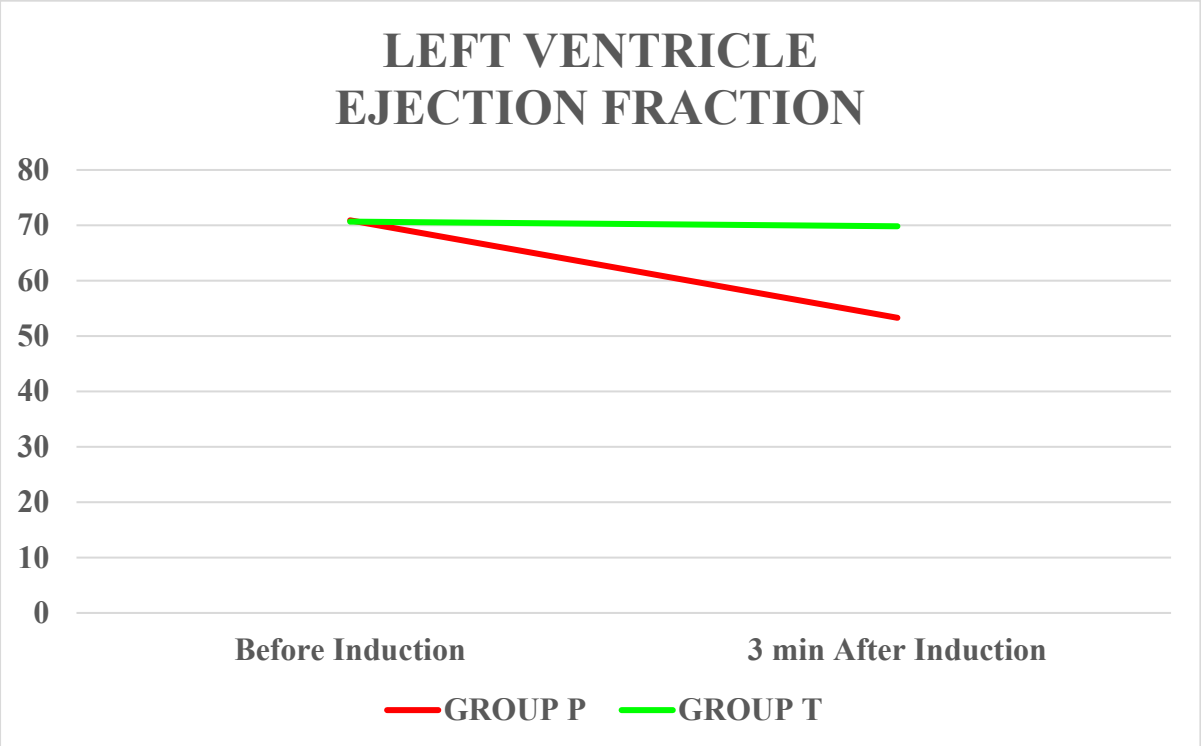
GRAPH 18: Effect on Left Ventricular Fractional Shortening

TABLE 19: Comparison of Effect on Left Ventricle Ejection Fraction between the two groups

LVEF (%)	GROUP P				GROUP T			
	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.
Before Induction	57	89	70.90	10.27	56	90	70.67	10.04
After Induction 3 min	25	86	53.30	14.21	54	90	69.83	9.52

LVEF – Left Ventricle Ejection Fraction; S.D. – Standard Deviation; MIN- Minimum; MAX- Maximum

Statistically significant reduction of left ventricle ejection fraction (LVEF) in Group P as compared to Group T when measured 3 minutes after induction with a p-value < 0.0001. With a p-value of 0.93 the difference in ejection fraction prior to induction of general anaesthesia is not found to be statistically significant.



GRAPH 19: Effect on Left Ventricular Ejection Fraction

DISCUSSION

General anaesthesia administered for major surgeries is associated with haemodynamic fluctuations which are usually seen most during the period after administration of the induction agents[29] of which propofol and thiopentone are two of the most commonly used. These fluctuations influence post-operative outcomes such as acute kidney injury, major adverse cardiac events, stroke etc[10,42]. Laryngoscopy and intubation performed during general anaesthesia also influence haemodynamic parameters enough to affect heart and brain[37]. Administration of opioids such as fentanyl help in decreasing his effect[37].

While propofol has surpassed thiopentone in popularity as an induction agent ending a reign of over fifty years, concerns regarding its haemodynamic effects remain with the quest for understanding, avoiding and/or controlling these effects endure.

Although studies have been conducted previously to evaluate the haemodynamic responses to propofol and thiopentone, more often than not they differ in patient selection, drugs and dosages administered and monitoring techniques etc[3,39]. Such differences among the studies conducted on this topic have made direct comparisons challenging to say the least[3,39].

Our study is a randomised clinical trial conducted at the Department of Anaesthesiology, KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre between April 2021 to March 2021. The study was conducted on sixty adult volunteers between the ages of 18 to 60 years posted to undergo non-cardiac surgeries under general anaesthesia. The volunteers were enrolled prospectively and randomly distributed into two groups of thirty each with a help of a computer-generated randomised table. Group P included individuals in whom general anaesthesia was induced with the combination of Propofol-Fentanyl while those in Group T

received Thiopentone-Fentanyl. Patients were pre-medicated with midazolam and vecuronium was used for muscle relaxation as these agents have been shown to have minimal effects on cardiovascular system[3].

Among the thirty individuals enrolled in Group P the number of males and females was equal at fifteen each. In Group T, thirteen were female and seventeen males. Mean age in Group P was 38.87 (±14.09) years while that in Group T was 36.70 (±13.79) years. In Group P, 73% individuals were classified as American Society of Anaesthesiologists Grade (ASA) I and 27% as ASA II. In Group T, 70% were ASA I and 30% were ASA II. The groups were comparable with respect to age, gender and ASA distribution.

Mean heart rate in our study showed a slight decrease in both the groups at the 3-minute mark with trend towards recovery at the 5-minute mark. The decrease was slightly more in Group P with mean heart rates declining from 86.47 ± 13.71 to 80.27 ± 11.39. However, this difference was not found to be statistically significant (p 0.18). This is in line with previous studies where slight increases in heart rate have been reported with thiopentone[3,14]. The greater degree of decrease in heart rate with propofol as observed by us is also consistent with previous studies conducted by Aun and colleagues[16] in children and Sørensen et al[4] in the elderly age group. Dalla et al[9] while studying effects of haemodynamic responses of general anaesthesia and positive pressure ventilation with the help of TTE also observed a decrease in heart rate with propofol as induction agent.

We observed a significant drop in both systolic and diastolic blood pressures as well as the mean blood pressures at the 3-minute mark in Group P with p values < 0.0001, 0.034 and

0.007 respectively. In Group T also, a similar pattern was seen but the degree of decrease was much milder as compared to Group P. This is consistent with previously published studies by Hino et al[10], Claeys et al[22], Coley et al[40], Vohra et al[39], Grounds et al[19], Rolly et al[37], Harris et al[36], Uygur et al[5] and a retrospective review by Reich et al[29]. The results are also in agreement with studies conducted in the paediatric age groups by Gauss et al[3] and Wodey et al[46]. These decreases have been ascribed to the negative inotropic effects[3, 14], changes in afterload[3,40,48] and in case of paediatric age group, changes in heart rate[16] as well. However, most of these studies did not use opioids concomitantly except those by Hino et al[10], Uygur et al[5], Vohra et al[39] and Harris et al[36].

There is a paucity of clinical studies comparing effects of general anaesthesia induction on the heart with propofol or thiopentone based on echocardiography. At the same time, there is difficulty in making direct comparisons between them and our study owing to differences in populations studied, induction protocols, type of echocardiographic examination and the echocardiographic parameters used for evaluation. Most of the studies evaluating haemodynamic effects of these two drugs have relied on clinical parameters like heart rate, arterial pressure monitoring, invasive monitoring of central venous and pulmonary capillary wedge pressure and cardiac output monitoring with bioimpedance, thermodilution or radionuclide methods.

The primary objective of our study was assessment of left ventricular function in patients undergoing general anaesthesia with trans thoracic echocardiography (TTE). TTE was performed on all the volunteers prior to induction and 3 minutes after induction with measurement of LVESD, LVEDD, LV fractional shortening and LVEF measured in the

parasternal short axis view with M-mode. While no significant differences were found in the diameters of left ventricle, statistically significant decrease in LV fractional shortening ($p < 0.0001$) and LVEF ($p<0.001$) was observed in Group P as compared to Group T. This correlates well with the studies performed using these parameters in animals[11,12,28].

Our findings are also in line with studies conducted by Yang et al[1] who reported a significant reduction in myocardial function based on systolic and diastolic velocities measured with transthoracic echocardiography and Doppler Tissue Imaging when patients received propofol as induction agent. In this study, however, no significant difference was found in ejection fraction with propofol while a statistically significant temporary decrease was observed with thiopentone[1] at 3 and 5-minute marks. In our study we have observed a significant reduction in LVEF after induction with propofol as compared to thiopentone 3 minutes after induction. While we used combination of thiopentone-fentanyl and propofol-fentanyl during induction, Yang and colleagues did not use any opioids during induction[1]. Also, in their study, all echocardiographic data was measured prior to tracheal intubation[1] while we performed our examination post intubation. We have used M-mode in parasternal long axis view to measure our parameters and Yang and colleagues used apical 4-chamber view for collection of their data[1]. These differences in protocol may explain the differences observed.

The marked myocardial depressant effects of propofol, as compared to thiopentone, observed in our study are also in agreement with the conclusions drawn by Mulier et al[14] in their study performed by LV volumetric assessment with transoesophageal echocardiography.

Concordant with previous studies by Bilotta et al[38] and Wodey et al[46] apart from animal studies by Tanaka et al in hamsters[11], Chen et al in mice[12] no statistically significant changes were observed in the LVDD and LVESD in our study. While Bilotta et al studies effects of two different rates of injection of propofol[38], Wodey et al compared haemodynamic and cardiovascular effects of both propofol and thiopentone[46]. Dahlgren et al[27] found a gradual decrease in LVEDD during induction of anaesthesia. However, they used midazolam and fentanyl for induction of anaesthesia with pancuronium as muscle relaxant.

In the study conducted by Wodey et al[46], no significant difference is reported in fractional shortening and LVDD with propofol while significant decrease in LVDD is reported with thiopentone. This is in contrast with our findings where we have observed a significant decrease in LV fractional shortening with propofol while no significant difference has been observed in LVEDD in either group. One of the factors attributable for this difference in observation could be the demographic profile of study subjects. While, we have included adults aged 18-60 years, Wodey and colleagues performed their study in infants aged 12 months or less[46]. Induction in their study was performed without the use of opioids and measurements were taken prior to tracheal intubation at induction and 5 minutes later[46]. In our study, induction agents were used along with opioids and measurements recorded 3 minutes after induction and intubation, nearer to the peak action time of the drugs.

The statistically significant reduction in LV fractional shortening observed in our study with propofol also differs from the findings of Gauss et al[3] who found a reduction in LVFS with thiopentone. In our study, no significant decrease in fractional shortening was observed with

thiopentone. While we performed our study in adult patients using TTE, Gauss et al studied these effects in infants using transoesophageal echocardiography[3].

LIMITATIONS

Our study is not without its share of limitations. It is a single centre study with a limited population even though the age, gender and ASA distributions are fairly matched. All the echocardiographic examinations were performed by a single person both before and after administration of anaesthesia thereby limiting inter-observer bias but arguably introducing performer bias. The echocardiographic examinations were limited in scope owing to logistic and time constraints. Due to these reasons, arguably superior indices of LV function such as volumetric assessment could not be performed. The limited time period of observation post-induction and prior to incision has not allowed us to examine effects of these changes in the post operative period. Performing an echocardiographic examination just prior to induction of anaesthesia in the operating room may introduce the element of anxiety thereby affecting the cardiovascular parameters of a patient. Premedication to alleviate anxiety could perhaps be administered to preclude this effect. Also, this was an observational study with no interventions to address the effects observed.

CONCLUSION

We assessed the effects of Thiopentone-Fentanyl vs. Propofol-Fentanyl on left ventricular systolic function in patients undergoing non-cardiac surgeries under general anaesthesia using trans-thoracic echocardiography and found that Propofol-Fentanyl produces significant myocardial depression as compared to Thiopentone-Fentanyl.

SUMMARY

In this study titled "**COMPARISON OF EFFECTS OF GENERAL ANAESTHESIA INDUCTION WITH THIOPENTONE-FENTANYL AND PROPOFOL-FENTANYL COMBINATIONS ON LEFT VENTRICULAR FUNCTION ASSESSED BY TRANSTHORACIC ECHOCARDIOGRAPHY: A ONE YEAR RANDOMISED CLINICAL TRIAL**" we have performed assessment of left ventricular function with trans-thoracic echocardiography after induction of general anaesthesia with either Thiopentone-Fentanyl or Propofol-Fentanyl combinations.

Sixty volunteers aged between 18-60 years belonging to ASA grades I and II who met the inclusion criteria were studied. Echocardiography was performed after induction of general anaesthesia and measurements taken (LVEDD, LVESD, LV fractional shortening and LV ejection fraction) for all the volunteers. The observations were tabulated as per the groups assigned. The distribution of volunteers with respect to age, gender and ASA grade was comparable in the two groups.

In our study, we have observed a more pronounced depressant effect on the myocardium and its contractility when general anaesthesia induction is performed with Propofol-Fentanyl as compared to Thiopentone-Fentanyl. Thus, we can conclude that propofol should be used with extreme caution among populations more susceptible to cardio-vascular depression which may lead to myocardial injury. These would include elderly patients, patients with poor cardiovascular reserves such as those with pre-existing ischaemic or valvular heart diseases, those with conditions influencing cardiac function such as obesity, obstructive respiratory diseases etc.

Echocardiography is a useful tool in the anaesthetist's arsenal. It can and should be used both pre-operatively and intraoperatively to guide patient management including choice of anaesthesia.

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ANNEXURES

ANNEXURE 1 - INFORMED CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr. /Mrs. /Miss. _____ we are requesting you to enrol you in the study titled **"COMPARISON OF EFFECTS OF GENERAL ANAESTHESIA INDUCTION WITH THIOPENTONE-FENTANYL VS. PROPOFOL-FENTANYL COMBINATIONS ON LEFT VENTRICULAR FUNCTION ASSESSED BY TRANSTHORACIC ECHOCARDIOGRAPHY: A ONE YEAR RANDOMISED CLINICAL TRIAL"** conducted by **Reg No. BA0120012** Post Graduate in M.D. Anaesthesiology under the guidance of Professor, Department of Anaesthesiology, J.N. Medical College, Belagavi under KAHER, Belagavi.

Respected Sir/Madam, we request you to participate in our study as you are eligible for it. During the study you will be asked some questions regarding your medical history and you are supposed to answer to the best of your knowledge.

Your participation in this research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N. Medical College. If you decide to participate you are free to withdraw at any time.

Purpose of the study:

The purpose of research is to study the effects of Thiopentone-Fentanyl and Propofol-Fentanyl combinations as induction agents in general anaesthesia on the cardiac function in a non-invasive manner with the help of trans-thoracic echocardiography in the operating room by assessing LV dimensions and diameter during systole and diastole hence calculating the LVEF and fractional shortening.

Procedure Involved:

If you agree to enrol in my study, I will ask you present, past and family history. Then you will be clinically examined in detail. You will be allotted into one of the two groups randomly using computer generated software. **Group P** will include patients who will be administered Propofol-Fentanyl for induction of GA. **Group T** will include patients who will be administered Thiopentone-Fentanyl for induction of GA.

Prior to being shifted in the main operating room, you will be examined with Trans-Thoracic Echocardiography. After being shifted into the OT and being induced for GA with the drug combination as per your assigned group, Trans-Thoracic Echocardiography shall be performed again before the surgery begins.

Voluntary Participation/Withdrawal:

Taking part in the study is voluntary. You may choose not to enroll yourself in this study. Your decision will not change any health care services offered to you or your ward at K.L.E. S Hospital & MRC.

Risks:

There is no risk involved with echocardiographic examination.

Benefits:

Echocardiographic examination shall enable us to study the haemodynamic effects of the aforementioned drug combinations and thereby titrate them in other patients as per responses helping us to be prepared for predictable changes after drug administration and decide the suitability of specific drugs based on a patient's clinical and echocardiographic parameters.

Privacy and Confidentiality:

The only people to know that you are as research subject are you and members of the research team. No information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results:

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with your identity remaining confidential.

Financial Incentives for participation:

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator. The patient shall bear no cost for the purposes of the study.

Compensation:

In the event of injury related to the study, treatment will be made available through KLES Hospital and MRC, Belagavi. There is no compensation or payment for such medical treatment by law. If you get injured you may contact **Reg No. BA0120012** at Department of Anaesthesiology, J.N. Medical College.

Questions:

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact **Reg No. BA0120012**, Department of Anaesthesiology, J.N. Medical College, Belagavi or Professor, Dept. Of Anaesthesiology, J.N. Medical College, Belagavi.

If you have any queries about your rights as a study subject, you may call Dr. Harsha Hegde, Chairperson, JNMC IEC, Scientist 'D' Indian Council for Medical Research, National Institute of Traditional Medicine Belagavi, Mobile: +91-9480422500.

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH TRIAL

"COMPARISON OF EFFECTS OF GENERAL ANAESTHESIA INDUCTION WITH THIOPENTONE-FENTANYL VS. PROPOFOL-FENTANYL COMBINATIONS ON LEFT VENTRICULAR FUNCTION ASSESSED BY TRANSTHORACIC ECHOCARDIOGRAPHY: A ONE YEAR RANDOMISED CLINICAL TRIAL"

Mr./Ms./Mrs. _____ voluntarily agree for the participation of as a subject of study. By signing this consent form, I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read for me in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject/Guardian: _____

Date:

Witness Name: _____ Signature: _____

Investigators Name: _____ Signature: _____

Date:

Place : _____.

ANNEXURE 2 - PROFORMA

"COMPARISON OF EFFECTS OF GENERAL ANAESTHESIA INDUCTION WITH THIOPENTONE-FENTANYL AND PROPOFOL-FENTANYL COMBINATIONS ON LEFT VENTRICULAR FUNCTION ASSESSED BY TRANSTHORACIC ECHOCARDIOGRAPHY: A ONE YEAR RANDOMISED CLINICAL TRIAL"

GROUP ALLOTED: P T

Date of Examination : IP No. :

Name :

Age : Gender : Occupation :

Address :

PRE-ANAESTHETIC EVALUATION

Past History

Hypertension		**Arrhythmias**	
Diabetes Mellitus		**Valvular Heart Disease**	
Ischaemic Heart Disease		**Previous Surgeries**	

General physical examination

Weight		**Pallor**	
Height		**Icterus**	
Temperature (°F)		**Cyanosis**	
Pulse		**Clubbing**	
Blood Pressure		**JVP**	
Respiratory Rate		**Pedal Oedema**	

Systemic examination:

Respiratory System		**CNS**	
CVS		**GIT**	

PREOPERATIVE PHYSICAL STATUS ASA Grade I II III IV V

	Before Induction	After Induction		
		0 Min	3 Min	5 Min
Heart Rate				
Systolic Blood Pressure				
Diastolic Blood Pressure				
Mean Blood Pressure				
Oxygen Saturation				

	Before induction	After induction	
		0 Min	3 Min
LV End Diastolic Diameter			
LV End Systolic Diameter			
LV Fractional Shortening			
LV Ejection Fraction			

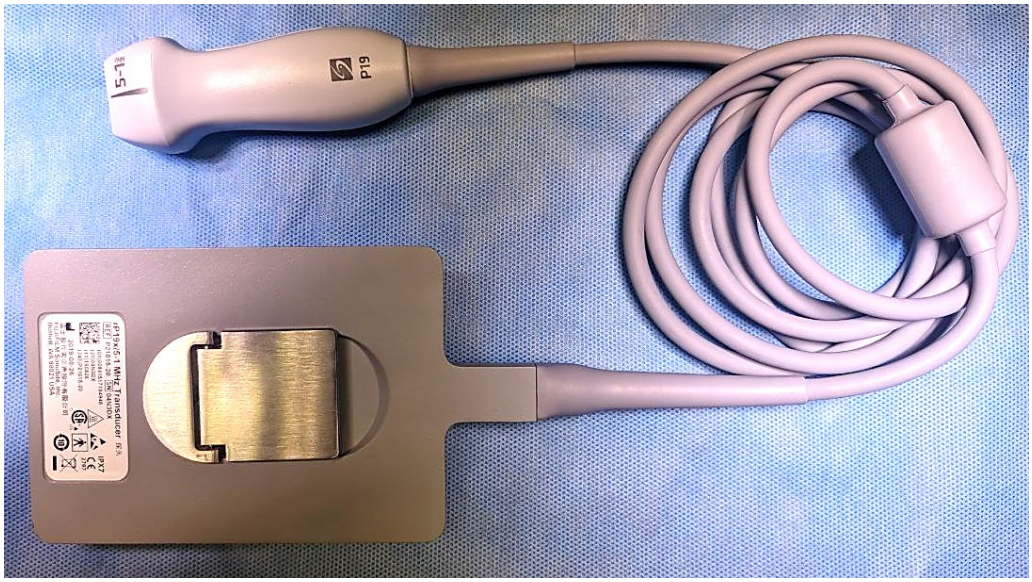
COMPLICATION	OBSERVATION
Desaturation	
Hypotension	
Arrhythmia	
Allergic Reactions	

INVESTIGATOR: _____

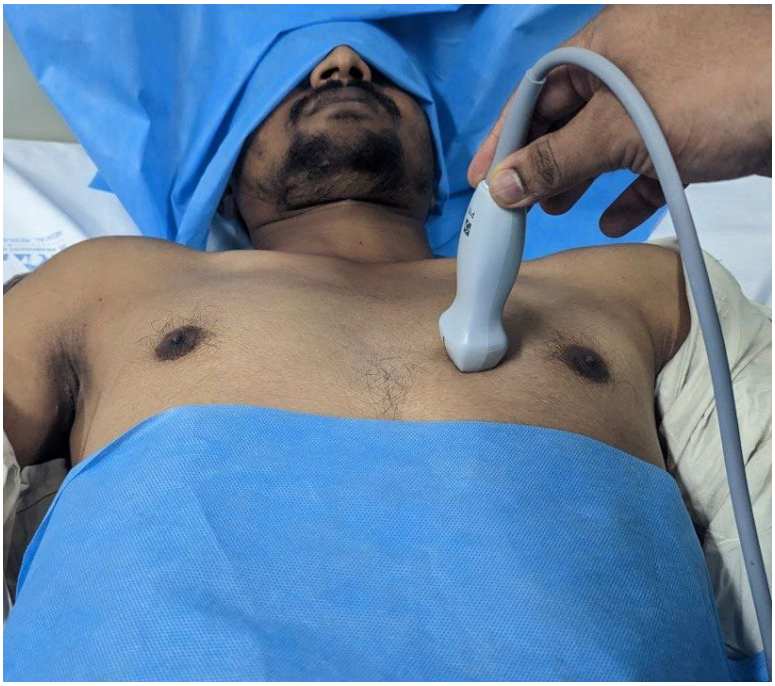
WITNESS: _____

ANNEXURE 3 - PHOTOGRAPHS

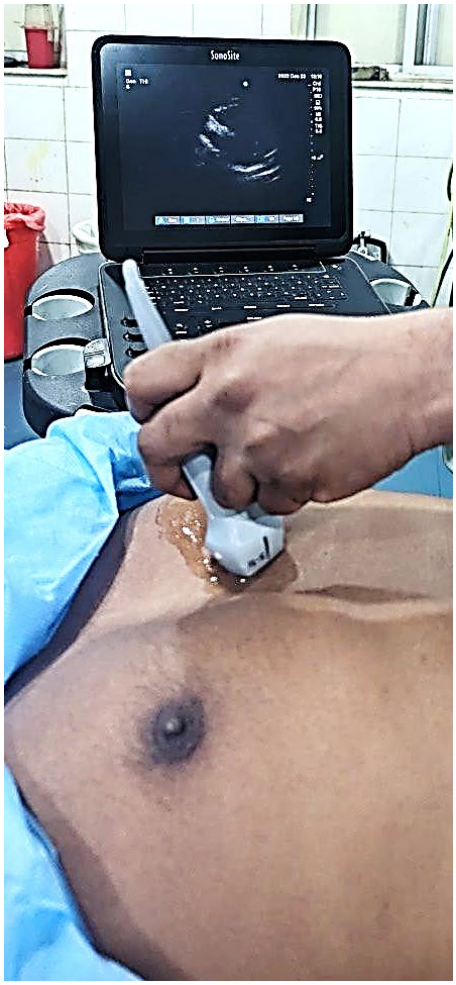
PHOTOGRAPH 1: Sonosite Edge II Total USG Machine

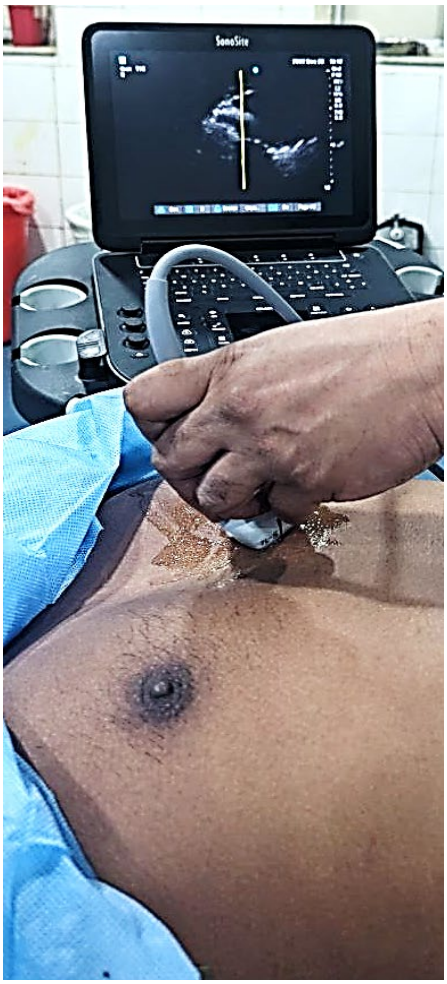


PHOTOGRAPH 2: P19 5-1 MHz Phased Array Probe

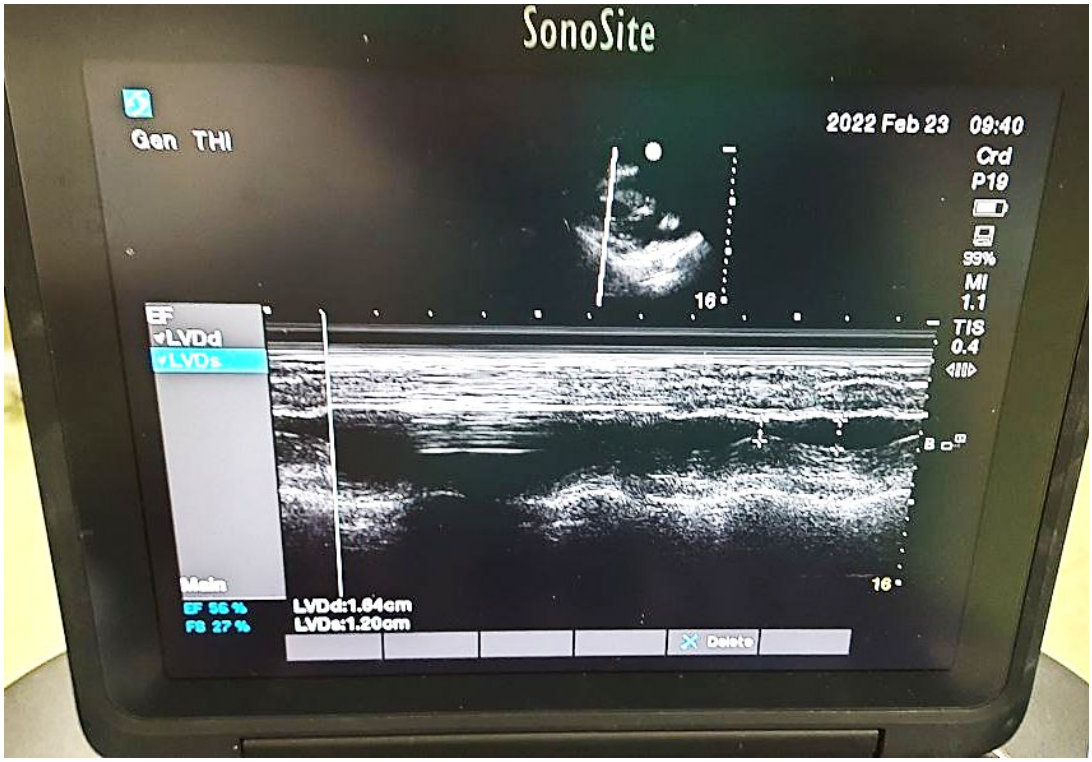


PHOTOGRAPH 3: Probe Position for Parasternal Long Axis View

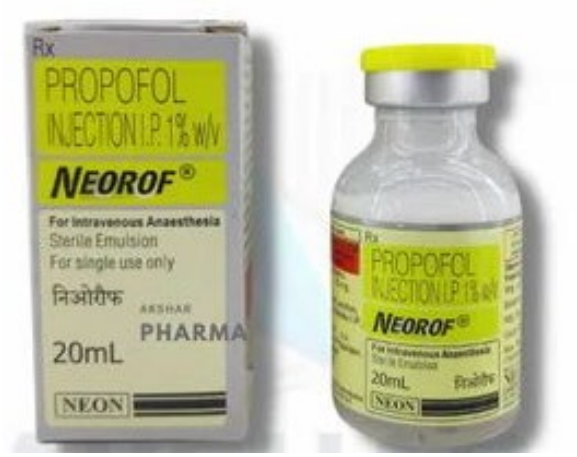




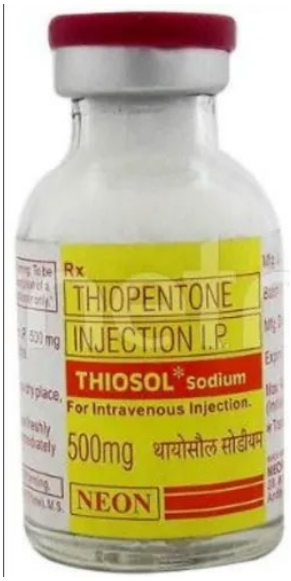
PHOTOGRAPH 4: Probe Position and Parasternal Long Axis View



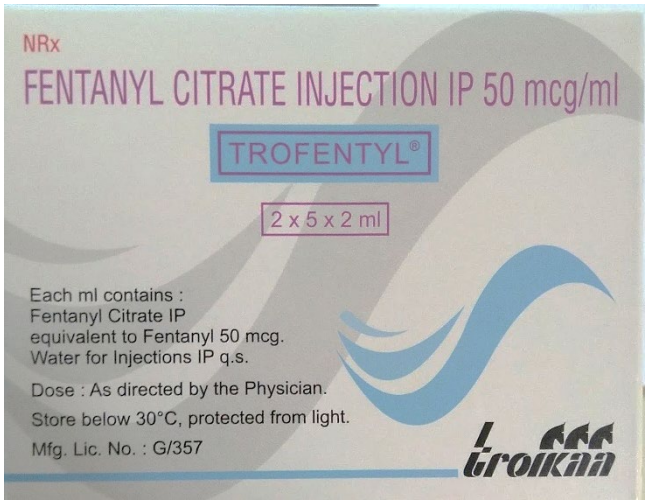
PHOTOGRAPH 5: M-Mode Echocardiography and calculation of Fractional Shortening and Ejection Fraction



PHOTOGRAPH 6: Injection Propofol



PHOTOGRAPH 7: Injection Thiopentone



PHOTOGRAPH 8: Injection Fentanyl Citrate

ANNEXURE 4 – MASTER CHART (GROUP-P)

GROUP P				STUDY PARAMETERS																									
S. NO.	AGE	SEX	ASA STATUS	HEART RATE (/min)				SYSTOLIC BLOOD PRESSURE (mmHg)				DIASTOLIC BLOOD PRESSURE (mmHg)				MEAN BLOOD PRESSURE (mmHg)				LEFT VENTRICLE END DIASTOLIC DIAMETER (cm)				LEFT VENTRICLE END SYSTOLIC DIAMETER (cm)				LEFT VENTRICLE FRACTIONAL SHORTENING (%)				LEFT VENTRICLE EJECTION FRACTION (%)			
				Before Induction	After Induction			Before Induction	After Induction			Before Induction	After Induction			Before Induction	After Induction			Before Induction				Before Induction				Before Induction			
					0 min	3 min	5 min		0 min	3 min	5 min		0 min	3 min	5 min		0 min	3 min	5 min		3 min				3 min				3 min			
1	50	M	II	90	90	74	70	140	136	120	124	92	86	80	80	108	103	93	95	3.68	3.36			2.7	2.71			27	20			60	48		
2	30	M	I	71	68	65	65	124	120	110	118	76	70	70	70	92	87	93	96	4.94	4.16			3.62	3.19			32	24			60	55		
3	35	F	I	86	85	92	95	124	130	116	100	82	84	68	63	96	95	82	75	2.96	1.87			1.92	1.35			35	27			66	28		
4	60	F	I	91	86	76	78	130	128	104	116	92	95	78	90	104	107	87	99	2.27	2.52			1.45	1.89			36	25			68	25		
5	45	F	I	78	80	68	70	140	138	90	93	80	80	55	61	96	95	66	70	1.58	2.27			1.13	1.89			28	17			59	37		
6	22	F	I	72	80	66	70	108	118	96	104	76	82	66	72	87	94	76	83	3.47	3.91			2.46	2.96			29	24			57	49		
7	59	F	II	88	86	80	86	140	134	104	126	94	90	82	86	109	105	89	99	2.16	2.16			1.35	1.59			38	26			70	55		
8	60	M	II	88	84	81	69	144	140	127	114	107	94	90	87	119	109	102	92	2.08	1.45			1.39	0.82			33	10			65	25		
9	28	F	I	84	86	70	80	114	110	94	106	82	78	70	74	93	89	78	85	3.38	2.7			2.34	2			31	26			60	53		
10	18	M	I	105	96	85	90	150	142	124	130	86	86	79	86	101	105	90	101	3.65	1.2			2.21	0.95			39	21			71	47		
11	46	F	I	118	106	105	110	124	121	63	103	85	85	43	71	93	94	48	79	2.39	3.47			1.01	2.33			58	33			89	62		
12	40	M	II	66	72	76	84	104	102	109	137	58	58	72	100	73	72	84	112	1.98	2.39			0.94	1.4			53	41			86	75		
13	53	F	II	71	75	82	72	127	101	107	95	92	73	76	72	104	83	87	81	3.97	2.58			2.71	1.76			32	22			60	47		
14	18	M	I	82	74	77	78	117	117	117	122	61	53	51	62	73	69	66	68	2.9	2.71			1.58	1.89			46	35			78	67		
15	26	M	I	97	76	75	67	115	107	93	96	78	75	52	69	87	82	62	73	1.95	1.64			1.07	1.13			45	31			79	63		
16	46	F	I	80	70	70	64	130	130	92	90	77	76	62	58	90	90	69	66	3.34	2.33			1.95	1.45			42	38			74	70		
17	58	M	I	59	78	70	70	164	142	101	116	98	88	75	95	116	106	84	104	1.95	2.96			1.13	2.39			42	19			76	41		
18	18	M	I	82	67	75	76	113	120	132	132	65	62	72	72	74	75	86	86	1.83	2.14			0.82	1.01			55	53			88	86		
19	20	M	I	69	98	77	80	126	139	118	124	75	55	61	103	89	77	78	111	1.3	2.96			0.88	2.18			32	26			65	53		
20	51	F	I	96	78	115	115	167	159	104	126	89	83	73	78	110	102	84	68	2.33	2.7			1.1	1.66			53	39			86	71		
21	19	F	I	85	76	74	82	124	106	107	106	76	62	62	62	92	72	74	72	3.02	2.33			2.02	1.7			33	27			63	55		
22	53	M	I	90	92	92	100	131	124	105	123	83	80	74	79	93	95	80	88	4.74	5.33			3.04	3.92			58	26			88	51		
23	38	M	I	97	82	80	80	134	129	120	113	93	86	79	77	106	98	91	87	2.52	2.14			1.7	1.64			33	24			63	49		
24	43	F	II	117	103	95	93	151	134	107	120	138	87	84	82	144	102	92	94	2.77	2.46			1.26	1.51			55	39			87	71		
25	37	M	II	99	102	87	83	134	128	108	117	82	80	78	81	96	96	89	91	2.27	0.88			1.45	0.63			36	28			68	60		
26	49	F	I	81	76	82	77	154	151	100	101	87	83	61	59	105	99	70	70	1.76	1.95			0.95	1.58			46	19			80	42		
27	27	F	I	90	86	72	78	126	118	100	108	78	74	58	64	94	89	72	79	2.14	2.58			1.39	1.58			35	29			67	58		
28	50	M	II	99	93	86	76	156	148	76	103	105	99	52	74	115	111	57	79	4.22	2.77			2.77	2.14			34	23			64	48		
29	41	M	I	88	92	90	112	144	140	96	110	86	80	68	70	105	100	77	83	1.64	1.64			1.07	1.2			35	27			68	56		
30	26	F	I	75	82	71	84	122	112	98	118	79	72	70	78	93	85	79	91	1.26	2.98			0.88	2.21			30	25			62	52		

ANNEXURE 4 – MASTER CHART (GROUP-T)

GROUP T				STUDY PARAMETERS																									
S. NO.	AGE	SEX	ASA STATUS	HEART RATE (/min)					SYSTOLIC BLOOD PRESSURE (mmHg)				DIASTOLIC BLOOD PRESSURE (mmHg)				MEAN BLOOD PRESSURE (mmHg)				LEFT VENTRICLE END DIASTOLIC DIAMETER (cm)				LEFT VENTRICLE END SYSTOLIC DIAMETER (cm)				LEFT VENTRICLE FRACTIONAL SHORTENING (%)				LEFT VENTRICLE EJECTION FRACTION (%)			
				Before Induction	After Induction				Before Induction	After Induction			Before Induction	After Induction			Before Induction	After Induction			Before Induction				Before Induction				Before Induction			
					0 min	3 min	5 min			0 min	3 min	5 min		0 min	3 min	5 min		0 min	3 min	5 min		3 min				3 min				3 min		
1	31	M	I	96	94	86	82		136	134	124	118	92	92	86	84	107	106	99	95	4.18	4.02	2.88	2.86	31	29	59	58		
2	45	M	I	80	86	82	80		124	120	114	118	76	72	66	70	92	88	82	86	2.6	2.33	1.95	1.76	25	25	58	56		
3	22	M	I	84	86	80	84		130	124	120	118	70	70	68	68	90	88	85	85	3.3	3	2.18	2.02	34	32	64	60		
4	31	M	I	86	84	80	75		136	136	134	133	80	74	84	83	92	89	96	96	2	2.98	1.35	1.98	33	34	64	64		
5	60	M	I	90	96	86	82		124	136	122	120	86	94	84	84	99	108	97	96	2.76	2.96	1.87	1.98	32	33	62	63		
6	52	F	II	100	94	81	100		100	99	91	97	52	52	46	55	64	64	57	65	2.44	2.24	1.51	1.4	38	38	70	70		
7	54	M	II	86	83	80	81		144	140	132	127	107	94	92	90	119	109	105	102	2.33	3.15	1.51	2.08	35	34	67	64		
8	30	F	I	120	121	92	140		112	123	108	105	79	86	62	72	90	95	76	84	3.02	1.64	1.7	1.01	44	38	76	72		
9	42	F	I	80	82	80	89		130	175	172	158	80	81	81	84	97	103	98	100	3.85	4.15	2.74	2.81	29	32	56	61		
10	21	M	I	113	109	99	100		114	111	99	112	54	51	53	61	69	63	63	72	1.27	2.08	0.86	1.31	32	37	65	70		
11	28	M	I	104	111	96	90		144	136	128	120	92	92	86	82	109	107	100	95	3.65	4.35	2.39	2.96	35	33	64	62		
12	31	M	I	87	97	116	81		137	145	133	116	75	118	87	79	90	125	101	90	3.02	3.65	2.14	2.65	29	27	58	54		
13	24	F	I	87	92	94	124		126	136	125	110	82	92	75	70	95	104	88	82	3.97	2.9	2.27	1.58	43	46	75	78		
14	33	F	II	114	116	113	110		185	191	187	159	107	162	92	77	124	170	114	98	1.7	2.27	0.8	1.07	53	53	86	86		
15	27	M	I	88	70	67	69		130	135	126	126	98	97	83	73	105	105	93	86	3.02	2.58	2.08	1.76	31	32	60	62		
16	26	M	I	67	63	70	82		120	117	110	109	70	84	62	65	86	95	78	79	1.07	1.83	0.5	0.82	53	55	88	88		
17	32	M	I	86	87	88	86		142	123	123	124	90	82	80	82	101	92	90	91	1.95	2.08	1.07	1.2	45	42	79	76		
18	19	M	I	60	66	78	84		141	132	120	132	81	74	64	82	94	87	77	94	2.58	2.33	1.39	1.45	46	38	79	70		
19	58	F	II	62	64	60	64		120	130	118	122	70	72	70	68	87	91	86	86	1.67	1.23	0.94	0.74	44	40	78	75		
20	52	F	II	61	62	77	80		154	140	129	126	97	99	95	101	116	112	106	109	2.46	1.95	1.01	0.9	59	46	90	90		
21	37	M	I	78	100	74	90		144	130	125	133	92	90	84	89	105	102	97	101	1.51	1.39	1.07	1.01	29	27	60	57		
22	60	M	I	65	53	48	57		95	106	104	103	62	70	69	62	70	78	76	71	2.9	1.89	1.64	1.13	43	40	76	74		
23	60	F	II	102	96	97	107		183	179	155	147	112	106	100	97	135	130	118	113	1.83	2.77	1.13	1.7	38	39	72	71		
24	20	F	I	96	122	118	98		118	94	106	111	80	54	63	74	89	61	74	82	1.89	2.14	1.01	1.32	47	38	81	71		
25	59	F	I	64	59	75	79		131	142	119	133	72	76	76	86	89	96	90	102	2.84	4.1	1.64	2.46	42	40	75	71		
26	25	M	I	65	62	71	67		127	129	116	109	77	81	77	68	93	67	90	81	2.58	3.21	1.45	1.76	44	45	77	78		
27	27	F	II	115	109	102	94		110	111	105	100	72	78	71	71	84	89	82	80	2.86	2.52	2	1.39	30	45	59	78		
28	38	F	II	94	88	99	83		139	136	131	135	102	92	104	92	111	106	111	107	3.09	2.96	1.64	1.58	47	47	80	80		
29	32	F	II	92	98	99	100		117	110	107	105	61	60	56	56	74	76	68	68	2.14	3.34	1.13	1.95	47	42	81	74		
30	25	M	I	49	69	67	63		155	145	137	106	112	93	60	68	112	106	77	78	2.65	2.58	1.83	1.76	31	32	61	62		

ANNEXURE 5 – KEY TO MASTER CHART

%	Percentage
/min	Per Minute
ASA	American Society of Anaesthesiologists
cm	Centimetres
F	Female
M	Male
mmHg	Millimetres of Mercury