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POST-OPERATIVE TROPONIN-T LEVEL AS A MARKER OF EXTENT OF MYOCARDIAL ISCHEMIC INJURY IN MITRAL VALVE REPLACEMENT SURGERIES

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CERTIFICATE

This is to certify that the dissertation entitled **"POST-OPERATIVE TROPONIN-T LEVEL AS A MARKER OF EXTENT OF MYOCARDIAL ISCHEMIC INJURY IN MITRAL VALVE REPLACEMENT SURGERIES"** presented here is the original work done by **DR.JOTHILINGAM.N** in the department of Cardiothoracic Surgery, Rajiv Gandhi Government General Hospital, Medical College, Chennai-600003, in partial fulfillment of the University Rules and Regulations for the award of Branch I M.Ch Cardiovascular and Thoracic Surgery degree under our guidance and supervision during the academic period from 2010-2013.

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DECLARATION

I, Dr. N. JOTHILINGAM, hereby solemnly declare that this dissertation titled "POSTOPERATIVE TROPONIN-T LEVEL AS A MARKER OF EXTENT OF MYOCARDIAL ISCHEMIC INJURY IN MITRAL VALVE REPLACEMENT SURGERIES" was done by me in the department of Cardiothoracic surgery, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-600003 during the period from March 2012 to March 2013 under the guidance and supervision of Prof. Dr. T.S.Manoharan,MS,MCh,. This dissertation is submitted to the Tamilnadu Dr. M. G. R. Medical University towards the partial fulfillment of requirement for the award of M.Ch. Degree in Cardiothoracic Surgery.

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INTRODUCTION

Cardiac surgery is often complicated by some degree of myocardial ischemic damage, despite much improvement in myocardial protection strategies and surgical techniques. But, precise markers that can easily and specifically identify and quantify the extent of such damage is lacking. Electrocardiographic changes are of limited value in the perioperative period. Trans-esophageal echocardiography may be helpful in assessing left ventricular function and regional wall motion (which are indirect indicators of adequacy of myocardial protection) but it lacks the sensitivity to detect subtle degrees of myocardial damage. But, it is very essential to identify perioperative myocardial injury and its extent because it directly affects postoperative outcome. Further, the assessment of such injury is helpful to compare different methods of myocardial protection and will be useful in perioperative management of patients.

The development and availability of Troponin assays are considered to be one of the most important innovations in the past decade in cardiac diagnostics. Cardiac troponins (Troponin-T and Troponin-I) are proteins that are present in the thin filaments of myofibrils. They are released into the circulation whenever there is myocardial damage. Cardiac troponins are specific for cardiac muscle and are not expressed in skeletal muscle fibers. Due to their high sensitivity and specificity, they are appropriate markers for perioperative myocardial ischemic injury.

But several studies, which have plotted the kinetics of the Troponins, have shown that cardiac surgery *per se*, causes elevation of Troponin levels in the blood even when there is no evidence of myocardial ischemic damage. This is because of surgical trauma to the myocardium. The level of increase varies with different types of surgeries and with different lengths of incisions. It is difficult to define a cut-off value for Troponin levels which will indicate a perioperative MI in patients who have undergone CABG, because

Troponin is universally elevated in all patients who undergo cardiac surgery. This rise is due to both surgical trauma and myocardial ischemic injury. Thus, the significance of Troponin levels in post-cardiac surgery patients is still ill-defined.

However, we hypothesized that if high Troponin levels result in poor postoperative outcomes (e.g. increased duration of ventilation, duration of ICU stay, duration of inotropic requirement, cardiac failure, mortality, etc.) and *vice versa*, that would indicate that Troponin is a reliable marker for extent of myocardial "ischemic" damage because pure surgical trauma alone (which is same for any single type of surgery) is not going to have any influence on these postoperative outcomes.

AIM OF THE STUDY

Our prospective study was thus designed to analyse the correlation between postoperative outcomes and Troponin-T level and to find out if there is any positive correlation between Aortic cross clamp time and Troponin-T.

If there is definite positive correlation between aortic cross clamp time and Troponin-T levels and between postoperative outcomes and Troponin-T levels, that becomes a definite evidence that this test is a viable and effective test in cardiac surgical field to assess the extent of myocardial ischemic injury.

REVIEW OF LITERATURE

HISTORY OF EVOLUTION OF THE CONCEPT OF MYOCARDIAL PROTECTION

Cardiac surgical procedures have been considered as unrealistic attempts even just 100 years back. Billroth and Paget have viewed cardiac surgery with skepticism. The first successful cardiac surgical procedure was the suturing of a stab wound in the right ventricle by Ludwig van Rehn in 1986. In 1902, Luther Hill performed a successful surgical procedure for a case of cardiac tamponade. These procedures, seemingly simple now, were performed one hundred years back as emergency resuscitative measures when cardiac surgery was unknown.

Frederick Trendelenburg performed experimental pulmonary embolectomy in animals using "inflow occlusion" technique. Kirschner, a student of Trendelenburg, performed a successful pulmonary embolectomy in a human in 1924 using the same inflow occlusion technique. The need for myocardial protection was not known at that time. The inflow occlusion was used just to get a bloodless field.

Alexis Carrel performed a descending aorta to coronary artery anastomosis in 1910 in a dog. He was able to finish this anastomosis within 3 minutes of interruption of circulation. But, the fact that the heart fibrillated within these 3 minutes and the dog subsequently died after 2 hours, made him conclude that the anastomosis should be completed within 3 minutes and this important observation led to the knowledge that the heart cannot withstand ischemia under fibrillating conditions.

Gibbon developed a cardiopulmonary bypass machine and started doing surgeries for congenital heart diseases in children. Due to repeated failures, he subsequently stopped using the machine.

Lillehei, using cross circulation, proved that heart surgeries could be feasible. CPB technology helped him perform successful surgeries and hence abandoned cross circulation after using it in 45 patients from 1954 to 1955.

During the next few decades, the concept of global organ protection evolved with the use of hypothermia. In 1961, Hufnagel and colleagues introduced the concept of myocardial cooling by ice slush.

Gradually, more complex cardiac surgeries were attempted. These procedures obviously needed longer periods of ischemia. Hence all these hearts suffered greater ischemic damage which was a great concern. Hypothermia was used to protect the heart from severe ischemic injury by lowering basal metabolic rate. But it did not provide a satisfactory protection for the heart. The concept of aortic cross-clamping was then applied. The heart stopped beating because of deprivation of high energy phosphate stores due to absence of blood supply. The cross-clamping technique greatly facilitated the surgery but at the same time making the heart prone to greater ischemic injury.

At this time, Melrose described that the heart could be arrested by chemical technique rather than by ischemic technique. He used potassium citrate to chemically arrest the heart and postulated that this preserves high energy phosphates in the heart and hence it is safe. But contrary to his expectations, this technique did not provide adequate myocardial protection and was in fact abandoned in many centers. Topical hypothermia was then added as an adjunct to this form of cardioplegia for better cardiac protection. In St. Thomas Hospital in London, Hearse et al. developed a solution, which provided reliable cardiac arrest and good myocardial protection.[1]

Gay and Ebert refined cardioplegia formulations in 1970s and 1980s. Follett and Buckberg described various strategies of cardioplegia delivery (temperature of cardioplegia solution, various routes of administration, etc). Buckberg found that blood was very useful

as a medium for cardioplegia administration. The composition of cardioplegic solutions continue to be modified worldwide according to various study reports proving superiority of one over another.

In 1978, Buckberg showed the importance of use of hyperkalemic reperfusate initially before aortic cross clamp is released.[2]

DAMAGE FROM MYOCARDIAL ISCHEMIA

Functional impairment of cardiac muscle in the absence of muscle necrosis is called myocardial stunning. This is usually a reversible phenomenon though it may last for few minutes to few days.

Myocardial cell necrosis occurs when the ischemic process is prolonged though the time duration beyond which necrosis of muscle fibers starts has not yet been defined. The extent of myocardial cell necrosis is strongly influenced by various myocardial protection strategies.

Contracture develops in cardiac muscle when ATP levels become critically low. This phenomenon is demonstrable in animals but uncommon in humans probably because the time to contracture is quite long in humans. The stone heart phenomenon usually starts in basal region of left ventricle and in subendocardium.

DAMAGE FROM REPERFUSION

Reperfusion damage to the myocardium is due to uncontrolled reperfusion i.e. reperfusion by unmodified blood and without control of flow or pressure.[2]

The mechanism of reperfusion injury involves free oxygen radicals and calcium influx into myocytes.

The event of myocardial damage sustained due to ischemia cannot be separated from that due to reperfusion injury because both are interdependent. But the surgeon has the unique opportunity to control these two events separately.

As the duration of ischemia prolongs, the myocardium undergoes the stage of myocardial stunning initially, and then myocardial necrosis. If ischemic process continues, stone heart develops, which usually indicates irreversible myocardial damage. This same course of events apply to reperfusion injury also.

In any one heart, different areas of myocardium may be different stages of ischemic injury. Usually patchy areas of necrosis are interspersed among normal areas of viable myocardium.

Microscopically, both apoptosis (programmed cell death without inflammation) and cell necrosis (cell death associated with inflammation) occur in post-cardiac surgical patients. Markus Malmberg, has demonstrated in animal studies that more the cardiac ischemic time more the degree apoptosis in cardiac muscle and also that ischemic preconditioning reduces the degree of apoptosis for any given duration of ischemic time.

VULNERABILITY OF THE DISEASED HEART

Hypertrophied heart is more susceptible to ischemic and reperfusion injury than a normal sized heart.

Chronic heart failure makes the heart more vulnerable to ischemic damage due to its already energy depleted state.

SURGICAL REQUIREMENTS

Cardiac operations can be performed when the heart is beating and it is being perfused or during induced ventricular fibrillation, but a precise and complete intracardiac surgical procedure requires a quiescent heart and a bloodless field. This would also prevent systemic air embolism. Hence aortic cross clamping becomes a necessity for most cardiac operations. So, myocardial protection becomes mandatory in order to prevent ischemic myocardial damage. Cardiac activity should be immediately stopped to prevent depletion of high energy phosphate stores. This is accomplished by chemical cardiac arrest by cardioplegic solution containing potassium.

Since aortic cross clamping and cardioplegic arrest of the heart are routine procedures in open heart surgeries and during aortic cross clamping the heart is deprived of its blood supply through coronaries, various standardized myocardial strategies have evolved over time to avoid ischemic damage to the myocardium during this period of myocardial ischemia. Some of them are projected to be superior to other techniques by various studies. But cardioplegic arrest of the heart is the gold standard against which others may be compared.

CARDIOPLEGIA DELIVERY METHODS

The goal of any technique of cardioplegia administration is to have uniform distribution of the solution to entire myocardium thus ensuring good myocardial protection. However, there is no single technique that is “best” for all circumstances. A practical knowledge of all the available techniques will help in special situations where other modes of cardioplegia delivery will be more useful than the conventional one in providing optimum protection to the myocardium.

Antegrade cardioplegia:

In this technique, the cardioplegia is administered through aortic root, coronary ostia or bypass conduits after completing distal anastomosis in CABG.

Most of the centers worldwide use the antegrade technique where cardioplegia is infused through aortic root because the technique is simple and efficient. It mimics the natural way of blood flow through coronaries. This method is not suitable in cases of aortic regurgitation or dissection in which aortotomy is done and the solution is administered through coronary ostia. Lifting or retraction of the heart (e.g. in Mitral valve surgeries) distorts the aortic valve and hence the heart must be repositioned before administering cardioplegia through aortic root.

Intermittent and continuous cardioplegia:

Continuous cardioplegia provides better myocardial protection but it is difficult to have a bloodless field in this technique and it also complicates the surgical field due to additional cannulae.

Retrograde cardioplegia:

It is helpful in patients with significant coronary artery stenoses where antegrade cardioplegia alone may not result in adequate distribution to entire myocardium. In this method, cardioplegia can be administered without interrupting the conduct of surgery. It is also useful for de-airing the coronaries and aortic root.

The right ventricle and posterior aspects of the septum are not adequately perfused by cardioplegic solution in this method due to proximity of their draining veins to the coronary sinus ostium.

It is also important to limit the retrograde pressure from 25 to 35 mmHg. Pressures of more than 50 mmHg will produce myocardial edema and hemorrhage.

Combined antegrade and retrograde cardioplegia:

This method provides the opportunity to gain optimum benefits of both antegrade and retrograde cardioplegias in a single patient.

Various compositions of cardioplegia solutions:

Basically two different types of solutions are described:

1. Extracellular or St. Thomas solution type
2. Intracellular or Breschneider solution type.

Extracellular solutions contain high sodium and calcium content with added magnesium. Intracellular solutions contain low sodium and calcium concentrations. Of these two types, the extracellular type is the most commonly used cardioplegia solution worldwide though some centers still continue to use intracellular type.

Each of these subtypes has been modified in their compositions and concentrations by different manufacturers.

Crystalloid and blood cardioplegia:

Crystalloid cardioplegia is simple, cheap and easy to prepare and administer. Blood cardioplegia provides the following benefits:

1. Ability to carry oxygen
2. Excellent buffering capacity
3. Scavenges free oxygen radicals
4. Electrolyte and osmotic compositions are similar to blood

Temperature of cardioplegia solution:

Cold cardioplegia (administered at 4 degree Celsius) is believed to provide better myocardial protection than warm cardioplegia (administered at 34-35 degree Celsius) though some studies have proved both of them to be equally effective. Tepid cardioplegia (28 degree Celcius) may provide advantages of both cold and warm solutions.

Additives in cardioplegia:

Since the potassium used in the cardioplegia is injurious to coronary vascular endothelium, additives are being tried which may reduce the dose of potassium to produce cardiac arrest.

Nicorandil, an ATP sensitive potassium channel opener, is one such agent used to reduce the dose of potassium in cardioplegia solution. This drug also prevents perioperative coronary spasm. It has also been proved to precondition the heart against subsequent ischemic injury.

L-arginine acts as a nitric oxide donor and helps in preventing endothelial dysfunction in ischemia-reperfusion injury. Its addition in cardioplegia solution has been shown to reduce postoperative Troponin-T release.[1]

ADDITIONAL STRATEGIES OF MYOCARDIAL PROTECTION:

Volatile anesthetic agents:

Volatile anesthetic agents (Isoflurane, Sevoflurane) have been proved to enhance myocardial protection by poorly understood complex and multifactorial mechanisms. They ameliorate the deleterious effects of free oxygen radicals in the phase of ischemia-reperfusion. In addition, they modulate potassium dependent ATP channels and produces

preconditioning effect. It has been shown that postoperative Troponin-T release is reduced with their use in anesthesia. Postoperative left ventricular function also is improved.

Acute Normovolemic Hemodilution (ANH):

This technique helps in better myocardial protection in two ways. First, it reduces requirement of blood transfusion. Secondly, it improves the rheologic characteristics of the blood and a reduction in hematocrit results in lower viscosity. This enhances myocardial blood flow to underserved areas of the myocardium.

Neutrophil depletion:

Neutrophils are associated with reperfusion injury by its release of destructive enzymes, free oxygen radicals and other toxic substances. Neutrophil depletion, either in CPB circuit or in cardioplegia solution has been shown to improve postoperative myocardial performance. Postoperative Troponin-T is also less in these patients.

Other medications useful in myocardial protection:

Erythropoietin, N-acetylcysteine, Desferoxamine and Statins have also been proved to enhance myocardial protection in some studies.[1]

ISCHEMIC PRECONDITIONING:

It is a phenomenon in which a previous sublethal ischemia to the myocardium provides protection against subsequent ischemic insults. In a study conducted by Ghosh et al. postoperative release of Troponin-T was less in those patients in whom ischemic preconditioning was applied.

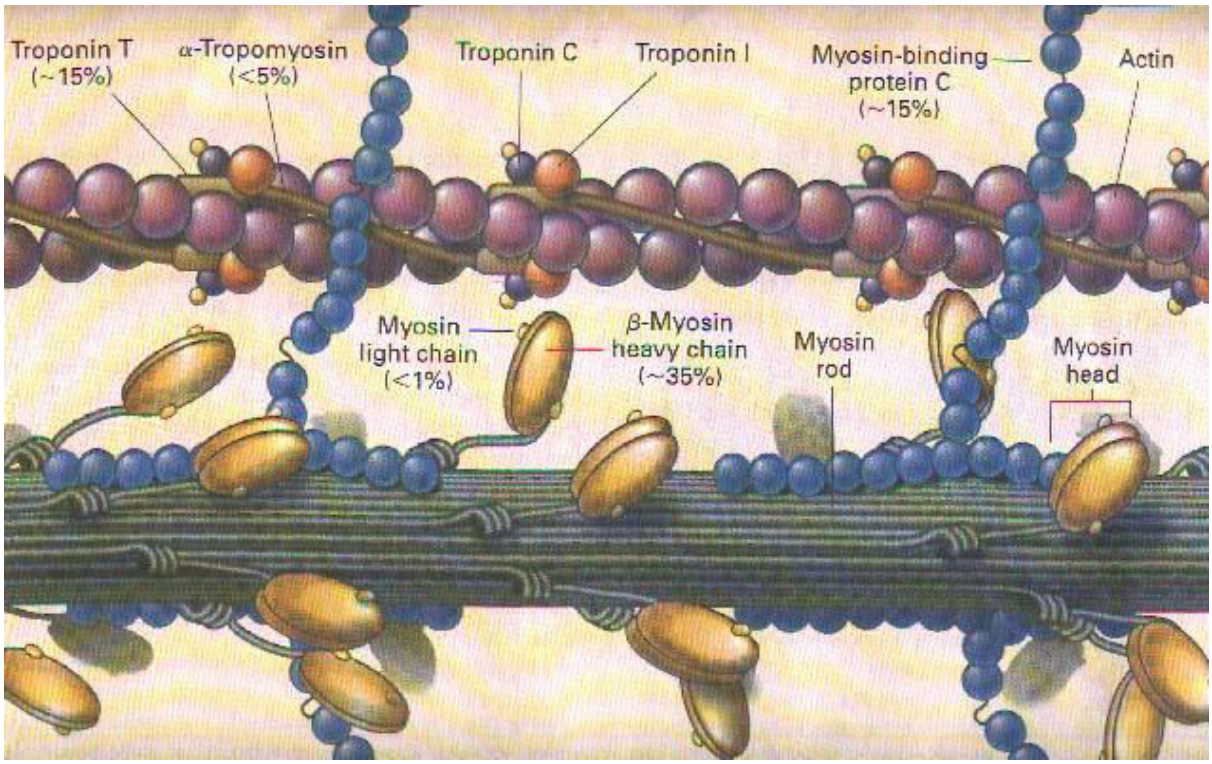
FIBRILLATION:

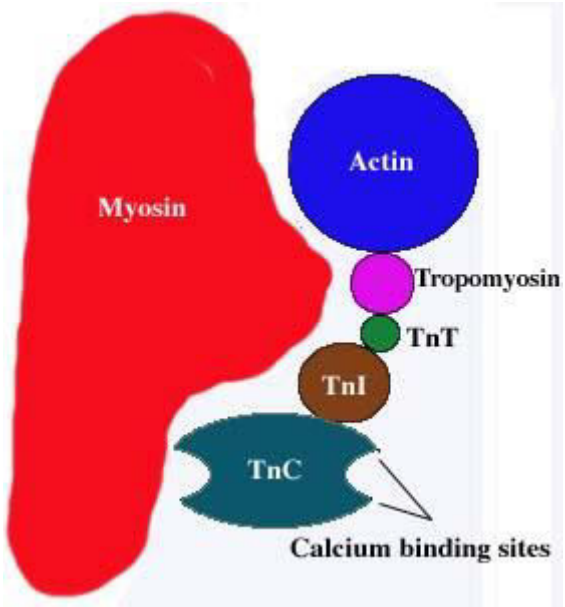
It is a useful, but less often used, strategy for myocardial protection. It relies on the principle of ischemic preconditioning. It is particularly useful in reoperative CABG surgeries where dissection and isolation of previous grafts and delivery of cardioplegia through them is difficult.

WHAT IS TROPONIN-T:

Troponin-T was discovered by Hugo A. Katus, a German physician. He subsequently developed a method to assay Troponin-T level.

The cardiac muscle is made up of myocyte composed of bundles of myofibrils which contain myofilaments. These myofibrils in turn are made up of repeating units of sarcomere. These sarcomeres are the basic contractile units of cardiac muscle. Each sarcomere is defined on either side by z lines. The sarcomere contains actin (thin filament) and myosin (thick filament). The interaction between actin and myosin and their sliding of one over another causes contraction and relaxation of cardiac muscle. Myosin has ATPase that hydrolyses ATP to provide energy for actin-myosin bridge formation. Thin filament is made up of three types of proteins: actin, troponin and tropomyosin. Actin is globular shaped protein arranged around rod shaped tropomyosin. Troponin proteins are attached to tropomyosin at regular intervals. 3 types of troponin proteins: Troponin-T, Troponin-C& Troponin-I (each coded by a separate gene). Troponin-T is attached to tropomyosin and troponin-C (which in turn is attached to Troponin-T) is the site for Calcium binding. During excitation-contraction coupling, calcium channels on sarcoplasmic reticulum open and calcium is released into sarcoplasm. These calcium ions bind to Troponin-C and bring about conformational changes in Troponin-T causing actin-myosin overlap. Troponin-I inhibits ATPase activity and thus inhibits the binding of actin and myosin and this inhibition is reversed by calcium attachment to Troponin-C.[3]





There are three tissue-specific subtypes of Troponin-T:

T1 in slow skeletal muscle fibers

T2 in cardiac muscle fibers (cTnT) and

T3 in fast skeletal muscle fibers.[4]

The clinical laboratories use assays to detect cTnT (cardiac Troponin-T). Hence, its detection is specific for cardiac origin. Specificity to cardiac origin is close to 98%. Current methods of cardiac Troponin-T assay have only 2% cross-reactivity to skeletal Troponin.

MECHANISM OF TROPONIN-T RELEASE DURING ISCHEMIC EVENTS:

Myocardial ischemic injury, either reversible or irreversible, causes increased permeability of myofibrils and thus Troponin complexes are released into circulation. Thus Troponin-T or Troponin-I assessment in blood indirectly detects myocardial ischemic damage.

Troponin is bound mainly to myofibrils (94%) and the rest 6% is cytosolic. When myocardial injury occurs, there is rapid early release of cytosolic Troponin-T and late gradual prolonged release from myofibrils. This affects the kinetics of Troponin-T release (Biphasic release pattern). The dissociation of that major portion that is compartmented in myofibrils is a time-consuming process and hence its long-lasting release. Though the serum half-life of Troponin-T is 120 minutes, this late and slow release of Troponin-T into the circulation is the reason for its values to remain high for upto 7-14 days.[5]

Myocardial depressive factors that are released in the setting of inflammatory states (e.g. sepsis, CPB) cause degradation of Troponin molecules into smaller molecules which escape into the circulation because of increased membrane permeability. [7]

ELIMINATION OF TROPONIN-T FROM BODY:

The exact mechanism of Troponin-T elimination from the body is unknown. It has been postulated that they are cleared by reticuloendothelial system (given the large size of these molecules). These large molecules are fragmented into small molecules and are

subsequently excreted by the kidney. A portion of them are also degraded by vascular endothelium.[8]

CAUSES OF ELEVATION OF TROPONIN-T IN CARDIAC SURGERY:

1. Direct surgical trauma,
2. Inadequate myocardial protection,
3. Reperfusion injury,
4. Myocardial infarction and
5. Cardioversion-defibrillation shocks

Other causes of elevations of Troponin-T [7]:

1. Acute pulmonary embolism
2. Acute pericarditis
3. Acute of severe heart failure
4. Sepsis and/or shock
5. Myocarditis
6. Hypertrophic cardiomyopathy
7. Type A aortic dissection
8. Strenuous exercise
9. Renal failure
10. Cardiac contusion after blunt chest wall trauma, external cardiac massage
11. False positive troponin- Heterophilic antibodies, Rheumatoid factor, Fibrin clots, Microparticles, Analyser malfunction

There are four different theories that explain the persistent basal elevation of Troponin-T in patients with chronic kidney disease and skeletal muscle disease.[8]

1. Theory of re-expression: in above said disease conditions, the cTnT re-expression occurs (a remembrance of early fetal form of expression)[20]
2. Theory of cross-reactivity: the skeletal form of Troponin-T cross-reacts with cTnT in the first generation assay methods. However, this is avoided in second generation assays where more specific antibodies are used.
3. Theory of isoforms: minimal amounts of isoforms of cTnT are expressed in skeletal muscles as well.
4. The kidneys have a role in clearance of Troponin-T from the body.[21]

TROPONIN-T IN CARDIAC EVALUATION:

The amino acid sequences of cardiac and skeletal forms of Troponin-T and I are different significantly and hence these two assays are useful in cardiac evaluation. But the structures of Troponin-C of both cardiac and skeletal muscle fibers are similar and so the assay of Troponin-C is not useful clinically.

ESC/ACC committee has documented that any degree of myocardial necrosis will impair the clinical course of the patient and that there is no threshold value of elevated Troponin-T below which it can be considered harmless.

It has been proved that even less than 1 gm of myocardial necrosis is detected by Troponin-T assay.[7]

SENSITIVITY OF TROPONIN-T:

Troponin-T is 95% sensitive for cardiac ischemic necrosis as it detects even subclinical levels of myocardial ischemic events (“microinfarcts”), which are not evident on ECG or ECHO findings.

SPECIFICITY OF TROPONIN-T:

With current methods of Troponin-T assay (2nd generation assays), the specificity of Troponin-T to cardiac origin is close to 98%.[11]

PATTERN OF ELEVATION OF TROPONIN-T:

Troponin-T level in blood starts to rise after 3-4 hours and peaks at 18-24 hours and lasts for 7-14 days in blood.[10]

PREVIOUS STUDY RESULTS:

Several studies have been conducted in the past in various parts of the world in similar manner as this study) to find out the significance of postoperative Troponin-T elevation.[12] Most of such studies have demonstrated positive correlation between higher Troponin-T values and increased postoperative morbidity and mortality. These studies have also derived a cut-off value for Troponin-T levels in post-cardiac surgery patients beyond which the morbidity and mortality is increased.

Most of such studies have been done on patients undergoing CABG. But, since adequacy of revascularisation and perioperative MI are major determinants of Troponin-T elevation in these kinds of patients, we didn't want to conduct a study on patients undergoing CABG surgery (because this study is aimed to find out whether Troponin-T in postoperative period reflects the inadequacy of myocardial protection). If, in this study, we had included CABG surgeries also, perioperative MI would have been a major confounding bias. Also, those patients who have evidence of significant Coronary Artery Disease were excluded from the study by conducting Coronary Angiogram in patients over 40 years of age. Those with ECG evidence of CAD were also excluded from the study.

Some other studies have been undertaken with similar intent, but by including various kinds of cardiac surgeries in a single study. Various kinds of cardiac incisions in various parts of the heart and various lengths of incisions cause various levels of elevation of Troponin-T. Atrial incisions cause lesser level of Troponin-T elevation when compared to incision on ventricular muscle. Hence, mitral valve replacement surgery (MVR) alone was taken for this study, by which we have avoided an important bias.

Sigismond Lasocki, analysed 502 consecutive patients who underwent various cardiac surgical procedures, and found that high Troponin-T value is an independent risk factor for postoperative mortality.[13]

Hugo A katus et al, performed a study on 338 patients and showed that Troponin-T improves the efficiency in diagnosis of myocardial ischemia when compared to CK-MB. (sensitivity of Troponin-T was 94% and that of CK-MB 63%)[13]

Bernard L Croal, conducted a study in 1365 patients and showed that elevated levels of Troponin-T at 24 hours after surgery was associated with increased short-term, mid-term as well as long-term mortality.[14]

James L Januzzi conducted a study on 224 patients to find out the significance of CK-MB and Troponin-T in post cardiac surgery patients. He found that elevated Troponin-T level correlated well with post operative complications whereas the correlation of CK-MB was poor.[15]

Joost Swaanenburg conducted a study on 123 patients undergoing various cardiac surgeries and found that when cross clamp time extends beyond 1 hour, there is rapid rise in Troponin-T levels. He also demonstrated that Troponin-T elevation levels depend on the type of cardiac surgery. Off-pump CABG surgeries did not cause a significant rise in Troponin-T level whereas on-pump CABG and valve surgeries produced Troponin-T elevation. Of all kinds of surgeries, valve surgeries produced highest levels of Troponin-T.[15]

H A Katus et al conducted a study in 56 patients and found that Troponin-T level raises correspondingly with cross clamp time.[16]

Russel Hirsch et al, conducted a study on 56 pediatric patients and found that Troponin-T at 1 hour after surgery indicates the extent of myocardial damage and was predictive of difficult recovery.[17]

Steven E. Lipshultz et al, conducted a study on 51 pediatric patients and showed that elevated Troponin-T levels are predictive of myocardial damage and its level correlates with increased morbidity and mortality.[18]

Luc Jacquet et al, conducted a study on 117 patients and found that Troponin-T estimation after CABG was helpful to detect perioperative ischemia or MI and was superior to ECG findings in detecting early and mild ischemia.[19]

OTHER METHODS ASSESSMENT OF ADEQUACY OF MYOCARDIAL PROTECTION:

Adequacy of myocardial protection cannot be assessed directly but can only be assessed by indirect methods like ECG, Echocardiogram and by various factors that are influenced by myocardial protection.

ECG:

Though postoperative ECG may detect a significant myocardial ischemic injury by ST-T changes, minimal global ischemic injury is not always sufficient enough to cause such changes in ECG. Patchy distribution of areas of necrosis and partially viable myocardium amidst normal areas of myocardium is common after prolonged ischemic time.

ECHO:

Regional wall motion abnormality may be detected by transthoracic ECHO (TTE) or, more accurately, by trans-oesophageal ECHO (TEE). But this finding occurs only in severely damaged myocardium. Ejection fraction in the postoperative period, when compared to preoperative status, may provide a clue to significant ischemic damage, though it may be influenced by various other factors like inotropic supports, volume status, residual anatomic lesion, patient-prosthesis mismatch, fever, sepsis, etc.

Functional status:

NYHA classification of functional status is a good tool to compare pre and postoperative status. But the classification is based on one's own subjective feeling of wellness and it is not sensitive and specific enough to detect minor or even moderate degrees of myocardial ischemic injury. A poor NYHA status postoperatively may be due to not only cardiac function impairment but also pulmonary functional status, renal function, skeletal muscle system, central nervous system, liver function, hemoglobin level, nutritional status, psychological motivation, etc.

Mortality rate:

Severe myocardial ischemic injury may be a cause of or sometimes a precipitating factor for postoperative mortality. In studies involving large number of patients, it may be found that Troponin-T elevation is a risk factor for postoperative death occurring within 1 month. But, since the mortality rates of open heart surgeries are generally very low in most of the cardiac surgical centers, the use of mortality rate, as an indicator of poor myocardial protection, is difficult in small scale studies.

CK-MB:

Since these enzymes are found in skeletal muscle as well, the assay of CK-MB is not sufficiently specific for cardiac origin. CK-MB used to be the commonly used cardiac marker earlier, till the arrival of Troponin-T assay. This test was widely used by cardiologists in acute coronary syndromes before the advent of Troponin-T. Since Troponin-T assay is now available in most of the hospitals, the use of CK-MB has come down.[15]

CK-MB is not specific to cardiac muscle because there is significant overlap between cardiac and skeletal muscle CK structure. Hence CK-MB assay is not as reliable as Troponin-T for assessing extent of myocardial ischemic injury.

It has been proved in studies that even with a transient myocardial ischemia which causes "reversible" myocardial damage, Troponin-T is released into circulation. This proves the high sensitivity of Troponin-T assay in detecting myocardial injury.[7]

INTRA-OPERATIVE MONITORING OF MYOCARDIAL PROTECTION:

These are the techniques used to monitor both adequacy and uniform distribution of cardioplegia. Myocardial temperature and pH monitoring are the two mainstays of intra-operative monitoring of adequacy of myocardial protection.[1]

Myocardial Temperature monitoring:

Thermocouple needles inserted into the myocardium is the most commonly used technique. Usually a single needle is inserted into the septum and the temperature is monitored. The adequacy of cardioplegia solution is dictated by the temperature attained at

the septum. When rewarming of the septum occurs, it becomes an indication for repeat cardioplegia.

Myocardial pH monitoring:

pH monitoring is not used widely but it is a useful tool to monitor adequacy of myocardial protection. pH monitoring can be done either directly by small pH meters inserted through the myocardium or indirectly through measurement of pH in coronary sinus effluent.

Research level assessment of adequacy of myocardial protection:

For experimental purposes, myocardial biopsy can be taken from animals that are subjected to aortic cross clamping either by transvenous route when the animal is alive or by postmortem studies when the animal is sacrificed. In humans, postmortem biopsies of myocardium may be examined for patchy muscle necrosis, myofibrillar degeneration, etc. for research purposes.

IMPORTANCE OF OUR STUDY:

Since poor myocardial protection and the injury sustained due to ischemia-reperfusion injury has its effects in both immediate postoperative period (unstable postoperative period, prolonged ventilator support, increased inotropic support, prolonged ICU stay, increased mortality rate) as well as in long term results (poor functional class, poor LV function, early mortality), its avoidance will result in overall improvement in patient's postoperative status and also a reduction in mortality. The identification of presence of myocardial ischemic injury and its extent in every individual patient will help to self-evaluate the techniques we follow in myocardial protection. If there is a single test which detects both the presence and the severity of myocardial injury specifically and with 100% sensitivity, that test can be used to evaluate all patients postoperatively both to find

out the cause of poor hemodynamic status as well as for research purposes to evaluate the efficacy of different methods of myocardial protection and different kinds of cardioplegic solutions.

Of all the tests available so far in this category, only Troponin-T evaluation has highest sensitivity and specificity.[9] But the important factor of surgical myocardial injury complicates the practical use of this test. Any surgical incision on the heart causes release of Troponin-T into the circulation and hence Troponin-T elevation is universal after any cardiac surgery. It is important to differentiate Troponin-T elevation due to ischemic damage from that due to surgical incision. Many scientific papers have been published about the significance of Troponin-T values in postoperative period. These papers have proved a fact that the rise of Troponin-T in postoperative period follows a predictable pattern i.e. the initial rise upto a certain level can be considered to correspond to surgical injury and later phases of elevation beyond this level indicates the level of myocardial ischemia-reperfusion injury.

The significance of Troponin-T after cardiac surgery still remains undefined.

This study that we have undertaken is another attempt to find out if the Troponin-T level predicts the severity of ischemic injury differentiating it from surgical injury based on a cut-off value between the two. In other words, our aim was to find out if Troponin-T elevation in post-cardiac surgery patients is predictable or is erratic without any predictability. (by the word “predictable”, we mean “predictable level of troponin-T consistent with the severity of ischemic myocardial injury”)

USEFULNESS OF TROPONIN-T IN CARDIAC SURGICAL PATIENTS:

Troponin-T should be routinely used after open heart surgeries for following reasons:

1. The value of Troponin-T in a postoperative patient tells us about the efficacy of myocardial protection strategies applied in that patient and to review any deficiencies in myocardial protection. In a long term basis, this would help improve the myocardial protection strategies that we follow in our hospital.

2. This test is useful to find out the cause of difficult postoperative period in some patients (unexplained postoperative hemodynamic instability).

3. Identification of high risk patients by high Troponin-T values may direct us to take special care in these individuals so as avoid morbidity or mortality. More duration of intensive care monitoring, special interventions and efficient use of economic resources may be directed to these high risk patients. By these measures, the patient outcome may be improved.

THE NORMAL CUT-OFF VALUES FOR TROPONIN-T:

The cut-off values for Troponin-T for detecting acute cardiac ischemic events (non-surgical) are well known but these values are not applicable for cardiac postoperative status because Troponin-T levels are invariably elevated in all patients undergoing cardiac surgery, irrespective of the complexity of surgery. Hence we need to find out the cut-off value for Troponin-T in post cardiac surgery status (specifically for each type of cardiac surgery). Below this cut-off level, the values would indicate incisional elevation and beyond this, would indicate ischemic necrosis.

The standard textbook in cardiology, Hurst's The Heart, denotes the normal and abnormal values for Troponin-T as below:

upto 0.01ng/ml (normal)

Upto 0.09 (borderline)

>0.1 (Indicative of myocardial infarction).

But, these values are not applicable to patients who have undergone cardiac surgery as the postoperative values of Troponin-T are usually much exceeded than 0.1ng/ml. Hence, new cut-off values should be derived for cardiac surgical patients, (more specifically, cut-off values for each type of cardiac surgery). Many previous studies have found that when the levels go beyond 13ng/dl, the mortality rate goes steeply high.

TROPONIN-T ASSAY METHOD:

Troponin-T in blood is assessed by immunometric one-step sandwich technique. The testing is based on polyclonal antibodies specifically developed against epitopes on cTnT molecule. These epitopes differ significantly between cardiac Troponins (cTnT) and skeletal Troponins.

In this method, polyclonal antibody to epitopes of cardiac Troponin-T is immobilized in polyvinylchloride test tubes. Troponin-T standards (control) or serum samples and peroxidase-labeled anti-Troponin-T monoclonal antibody is added to these test tubes. When incubated, Troponin-T molecules are adsorbed onto polyclonal antibody (which are in solid-phase) and to monoclonal antibody-enzyme complex (which are in liquid phase). The unbound peroxidase-labeled monoclonal antibodies are removed by washing. Now, the antibody-enzyme complexes which are adhered to the tubes correspond to Troponin-T level in that patient. The amount of enzyme immobilized is the direct measure of bound Troponin-T and this is measured by spectrophotometer (by peroxidase substrate conversion at 405 nm wavelength).[13]

DETAILS OF THE STUDY

The study was intended to find out if Troponin-T assay in postoperative status was useful as an indicator of myocardial ischemic injury sustained during aortic cross clamp and cardioplegic arrest.

To analyse the correlation between myocardial ischemic injury and Troponin-T level, we decided to correlate the following variables with the level of Troponin-T.

1. Aortic cross clamp time
2. CPB time
3. CP interval time
4. Longest Time Off Cardioplegia (LTOC)
5. Average Time between each cardioplegia (ATOC)
6. Postoperative duration of ventilation
7. Duration of ICU stay
8. Inotropic support required
9. Post op ECG evidence of myocardial ischemia
10. ECHO evidence of myocardial ischemia
11. Clinical evidence of failure (evidence of pulmonary edema, requirement of excess diuretics, etc)
12. Postoperative functional status(NYHA)
13. Mortality

The mortality rate following open heart surgeries are too low to be used as a marker of poor surgical results in a small scale study. Hence, we depend on other evidences of myocardial injury to establish correlation between poor myocardial protection and poor postoperative outcomes.

EXCLUSION CRITERIA:

Those patients with severely depressed cardiac function (EF<40%) require special care during myocardial protection measures. And also there is a rise in Troponin-T level in blood of patients in failure. Hence these patients were excluded from the study.

As already mentioned, those patients who have evidence of coronary artery disease (ECG or Echo evidence) were excluded from the study since perioperative MI may cause a rise in Troponin-T elevation. Patients older than 40 years are routinely evaluated with coronary angiogram and those who have significant coronary artery disease are also excluded from the study.

Patients who had already undergone Closed Mitral Commissurotomy (CMC) and now undergoing mitral valve replacement surgery were excluded, as during dissection of adhesions, direct surgical injury to myocardial tissue occurs.

Patients with more than mild AR were also excluded.

Since Troponin-T elevation occurs in patients with chronic renal failure due to unknown reasons (explained below), CKD patients were excluded from the study.

Patients with elevated liver function tests were also excluded since the excretion of Troponin-T may be affected in these patients.[7]

THE TIMING OF THE TROPONIN-T ESTIMATION IN THIS STUDY:

Since Troponin-T levels usually reach their peak values at around 18-24 hours after an ischemic event, and then start to decline, a single estimation of its value at 24 hours is used in this study. Most of the previous studies to evaluate the correlation of Troponin-T with myocardial ischemic time have used this same kind of testing (i.e. a single measurement at 24 hours after surgery, though some of the studies have done Troponin-T assay at 20 hours)

It has been proved in studies that even with a transient myocardial ischemia which causes "reversible" myocardial damage, Troponin-T is released into circulation. This proves the high sensitivity of Troponin-T assay in detecting myocardial injury.[7]

THE STANDARD STEPS OF A MITRAL VALVE REPLACEMENT SURGERY IN OUR HOSPITAL:

Under General Anesthesia, median sternotomy is done. Thymus is mobilized. Pericardial cradle is created. Cardiopulmonary bypass is established with bicaval and aortic cannulae after heparinisation. Alpha-stat acid-base management protocol is followed. Heparin is administered at a dose of 300 U/kg body weight. Activated Clotting Time (ACT) is tested after 5 minutes and it is maintained above 480 sec throughout cardiopulmonary bypass. Priming solution (for an adult) is prepared by adding 500ml of Ringer-Lactate solution + 500ml of Hetastarch . 100ml of Inj.Mannitol (20%), 50 ml of Inj.Sodium Bicarbonate and 2ml of Inj.Dexamethasone are added to this solution. Heart is cooled to 32 degree Celsius gradually over 5 minutes. Aorta is cross clamped at 32 degree C. Antegrade cardioplegia is administered through a 12 Fr cannula in the ascending aorta with digitally guided aortic root pressure, for a duration of 2-3 minutes. Cardioplegic solution is prepared with Inj.Plegiocard. 4:1 blood cardioplegia is prepared. This solution is administered at 4 degree Celsius. The left atrium is opened to avoid distension of the left heart. After cardioplegia administration and electromechanical quiescence of the heart is obtained, ice slush is poured into pericardial cavity and its spread underneath the heart is ensured. Cardioplegia is repeated every 20-30 minutes or upon seeing the cardiac activity, depending on whichever is earlier. Ice slush is applied after every cardioplegia administration. When the surgery is predicted to be over within 10 minutes ice slush is avoided during the last cardioplegia. Core cooling is done upto 28 degree Celsius. Once left atrium is opened, any clot in the cavity or in LA appendage is removed. LA appendage exclusion is done, in

patients with LA/LA appendage clot, with circumferential sutures taken on endocardial side of LAA using 3-0 prolene. Anterior mitral leaflet (AML) and posterior mitral leaflet and subvalvular apparatus are examined. PML is fully or partially preserved if anatomy is favorable. AML and its chordate are removed. Intermittent horizontal mattress sutures are taken from atrial side (so that the pledgets lie on atrial side and the valve lies intra-annularly) using 2-0 Ethibond pledgetted sutures with 13 mm round-bodied half circle needles. The valve sizer is used to measure the annulus size and valve is selected according to it. Selection of tilting disc or bileaflet valve depends on surgeon's preference as well as the availability of valve at that time (valves being supplied by the TNMSC). All the suture needles are subsequently passed through the sewing ring of the prosthetic valve and the valve is parachuted to the annular position. The sutures are tied securely with 5 knots. After mitral valve implantation, the mobility of the prosthetic valve leaflet(s) is tested. Any subvalvular chordae or other structure interfering with the movement of the leaflet is cut away or else the valve is rotated within the sewing ring such that the mobility is unrestricted. Usually, a tilting disc valve is positioned with its larger orifice facing posteriorly if PML was excised and anteriorly if PML is preserved. A bileaflet valve is positioned in anti-anatomical position. Left atrium is closed in two layers using 3-0 prolene and before tying the last knot, the LA is de-aired. The CP cannula in ascending aorta is used for de-airing and blood is allowed to be ejected through this for 5 minutes and later it is connected to pump with 300ml/min reverse flow. Aortic cross clamp is removed with head end down and with carotid compression and with the pump flow reduced to 0.5 lit/min. This flow rate is gradually increased to normal flow over 2-3 minutes. Defibrillators are used when necessary. The heart is supported with pump for a duration of 1/3rd of total cross clamp time. Heart is weaned from cardiopulmonary bypass gradually. CP cannula, SVC and IVC cannulae are removed and Protamine infusion is started. When half of the protamine infusion is completed, aortic cannula is removed. Protamine dose is calculated according to

the total dose of heparin given during the surgery (1.2mg for 1mg of heparin) also considering the ACT value and the time interval between heparin administration and protaminisation. Intercostal and/or mediastinal drainage tubes are placed. After hemostasis, sternum is approximated with 6 metric steel wires (in an adult); subcutaneous layer approximated with 2-0 Vicryl and skin with subcuticular absorbable sutures. The inotropic support is started only when it is indicated according to the hemodynamic status and not on a regular basis. Postoperatively, patient is shifted to Intensive Care Unit where each patient is cared by a single nurse.

CARDIOPLEGIC METHOD FOLLOWED IN OUR INSTITUTION:

Antegrade, intermittent, cold and blood cardioplegia is the routine cardioplegia method followed in our institution for all cases of Mitral Valve Replacement (MVR) surgeries. 4:1 blood cardiolplegia is administered at a dose of 20ml/kg for first time and then 10ml/kg subsequently.

ANESTHESIA:

Patients are given premedication and pre-operative antibiotics 30 minutes before surgery. Induction is done Inj.Thiopentone and Inj. Fentanyl is used as a narcotic. Inj.Vecuronium is used for paralysis. Inhalant anesthetic, Isoflurane is used at 1MAC. It has been proved in studies that Isoflurane has pre-conditioning effect on the heart and its use is associated with lower postoperative Troponin-T levels.

POST-OPERATIVE CARE:

Patients are monitored in cardiothoracic ICU where each patient is monitored by a single nurse. The team leader of the ICU is a cardiothoracic surgeon. Inotropic supports are not a routine protocol in our hospital but are started only on the basis of hemodynamic status. Patients are extubated when they are hemodynamically stable, fully alert and there is

no significant post-operative bleeding. Some of the surgical units have a protocol to extubate them only on the 1st post-operative day in the morning hours. Intravenous unfractionated Heparin (5000 units) is administered 10 hours after surgery if there is no significant drain and Acinocoumerol is started in the evening of 1st postoperative day. Patients are monitored in this ICU for minimum 2 days after surgery. When patient is stable, patient is shifted to step-down ICU where each nurse monitors 5 patients.

TROPONIN-T LEVEL ESTIMATION

Troponin-T analysis was done when 24 hours had passed after surgery. For this purpose, 2ml of blood is collected from the patient and is sent to the lab in a test tube (The cost of the test was borne by the prinicipal investigator). The testing was done in a private lab (Hi-Tech Labs) and all the 51 samples were analysed in the same laboratory. The blood sample was centrifuged immediately and the serum was used for estimation of Troponin-T level by Electro-chemiluminescence (ECLIA) method. The results are given in ng/ml units.

MATERIALS AND METHODS

This prospective study was undertaken as an analytical study to find out the significance of post-operative Troponin-T level as a marker of myocardial ischemic injury in mitral replacement surgeries, in cardiothoracic surgery department of Rajiv Gandhi Government General Hospital, Chennai-600003, from April 2012 to March 2013. Hospital Ethical Committee approved this study to be conducted in Rajiv Gandhi Govt General Hospital. Patients were well informed about the nature of the study and consent was obtained in written format for withdrawal of 2 ml of blood and Troponin-T estimation.

INCLUSION CRITERIA

Patients who were to undergo Mitral Valve Replacement Surgeries during the above said period were included in the study. Both Rheumatic and Non-rheumatic pathologies were accepted for the study. Both stenotic (MS) and regurgitant (MR) lesions (or a combined of two) were included. Only patients aged more than 13 years were included in the study.

EXCLUSION CRITERIA

1. Patients who have evidence of coronary artery disease
2. Re-do mitral valve surgeries (Post-CMC)
3. Poor left ventricular function (EF<40%)
4. LV diastolic dimension >7.0 cm
5. Renal failure
6. Hepatic failure
7. Patients with more than mild AR (aortic regurgitation)

METHODOLOGY

The preoperative, per-operative and post-operative details were personally collected by the investigator by direct communication with the patient and by assisting during the surgery and also following-up the patient in post-operative period. The data regarding significant events after discharge of the patients were also traced by phone communication and by follow-up in the out-patient department.

The information and data collected for each patient were entered in the proforma specially designed for this study.

The following information/data were collected from each patient.

1. Name, age, sex, IP number, Date of admission
2. ECG and Echo findings- Echocardiogram is done both by cardiologists and cardiothoracic surgeons.
3. Pre-operative functional class (NYHA classification was used)
4. Presence or absence of Atrial fibrillation
5. Total cross clamp time
6. Number of times cardioplegia was administered
7. Longest time off cardioplegia (Longest time between any two consequent cardioplegia)
8. Average time interval of cardioplegia (time interval between consequent cardioplegia doses)
9. Cardiopulmonary bypass (CPB) time
10. Requirement of DC shocks: it has been proved in studies that, though external defibrillator application causes elevation of Troponin-T, internal cardioversion does not cause any such elevation.

11. Requirement of post-operative inotropic support. This was classified into three categories for the purpose of ease of calculation and better understanding.

Drug	Minimal	Intermediate	High
Dopamine	<5ug/kg/min	6-10ug/kg/min	>11ug/kg/min
Adrenaline	<0.05ug/kg/min	0.06-0.1ug/kg/min	>0.11ug/kg/min
Isoprenaline	<0.05ug/kg/min	0.06-0.1ug/kg/min	>0.11ug/kg/min

12. Duration of inotropic supports (in days)
13. Duration of postoperative ventilation (in hours)
14. Duration of ICU stay (in days)
15. Duration of hospital stay after surgery (in days)
16. ECG or echo evidence of myocardial ischemia. A new q wave of more than 0.1 mV, or ST-T changes in two consequent leads suggestive of ischemia were taken as positive evidences of perioperative MI or significant ischemic injury. ECG interpretation was done by cardiologists in association with cardiothoracic surgeons. Postoperative echo was performed by cardiologists in the immediate post-op period if patient is hemodynamically unstable but only after 7 days if patient is stable.
17. Clinical evidence of failure: patient was examined by the investigator for presence of any signs of cardiac failure like, pulmonary crepitations, pedal edema, tachycardia, dyspnoea, mental obtundation, cold peripheries, high CVP, reduced urine output, etc., Patient's symptoms were also taken into account.
18. Ejection fraction of left ventricle: this was categorized into three varieties.

    EF 41-50% - mild dysfunction

    EF 31-40% - moderate dysfunction

EF <30% - severe dysfunction

19. Postoperative NYHA status: patients were classified into 3 categories: those who got improved after surgery and those who didn't get any improvement and those who got worsened after surgery.
20. Requirement of IABP
21. Mortality: the cause of mortality was assessed and was ascertained whether it is due to cardiac cause or non-cardiac cause.

ANALYSIS METHODS

Data were analysed with the help of a doctor specialized in statistics.

Descriptive statistics: mean± standard deviation was calculated.

Correlation for continuous variables was done. Chi-square/Fischer's test was done for categorical variables. Independent 't' test was done to look for significant different between 2 groups. ROC (Receptor Operator Characteristic) curve was used to determine the cut-off level of troponin-T at which levels, the postoperative complications occur more. By ROC curve, the level was fixed at 0.6 ng/ml.

Data was entered in Microsoft Excel Spreadsheet and was analysed using SPSS (Statistical Package for Social Science) version 16.

RESULTS

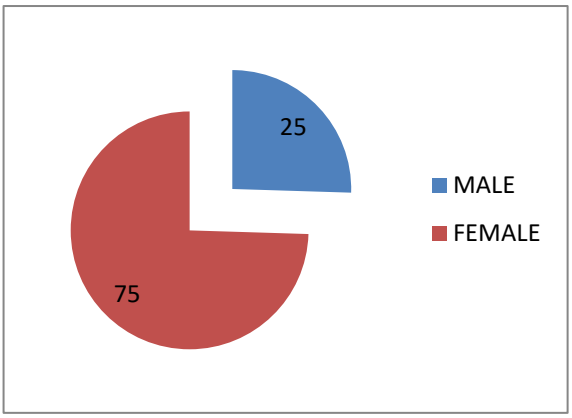
AGE DISTRIBUTION:

The Age group extended from 15 years to 61 years.

Mean age was **32.92 ± 12.02** years and median age was **32 years**.

SEX DISTRIBUTION:

Among the study participants, 75 % were females



LESION-WISE CLASSIFICATION:

16 (31.4%) patients had mitral stenosis

13 (25.5%) patients had mitral regurgitation

22 (43.1%) patients had both mitral stenosis and regurgitation

17 (33.3%) patients had pre-operative atrial fibrillation

2 (3.9%) patients had LA clot.

NUMBER OF CP (NUMBER OF TIMES CARDIOPLEGIA WAS ADMINISTERED):

1 – 1 (2%)

2 – 30 (58.8%)

3 – 18 (35.3%)

4 – 2 (3.9%)

Average: 2.4

Median: 2

For those patients, who received 1 or 2 cardioplegias, the average Troponin-T level was 0.676 ng/ml.

For those, who received 3 or 4 cardioplegias, the average troponin-T value was 0.706 ng/ml.

TOTAL CROSS CLAMP TIME:

Average: **68 ± 2 minutes**

Median: 70 minutes

Longest: 87 minutes

Shortest: 28minutes

Aortic cross clamp time	Number of patients	%	Average Troponin-T value for this group
≤70 minutes	27	52.9%	**0.567 ng/ml**
> 70 minutes	24	47.1%	**0.821 ng/ml**
Total	51	100%	

The above table shows that Troponin-T levels are elevated with increasing duration of aortic cross clamp time.

LONGEST TIME OFF CARDIOPLEGIA (LONGEST INTERVAL BETWEEN CARDIOPLEGIAS IN A SINGLE PATIENT):

Mean: 28 ± 1 minutes

Median: 28 minutes

Longest: 38 minutes

Shortest: 22 minutes

Longest Time Off Cardioplegia	Number of patients	%	Average Troponin-T value for this group
≤ 28 minutes	29	56.8%	**0.661 ng/ml**
>28 minutes	22	43.1%	**0.723 ng/ml**
Total	51	100	

The above shows that when the interval between two cardioplegias is prolonged, Troponin-T levels are simultaneously elevated.

AVERAGE TIME INTERVAL OF CARDIOPLEGIA:

Mean: 26 ± 1 minutes

Median: 26 minutes

Maximum : 34 minutes

Minimum : 21 minutes

Average interval between cardioplegias	Number of patients	%	Average Troponin-T value for this group
≤ 26 minutes	27	53%	**0.594 ng/ml**
> 26minutes	24	47%	**0.739 ng/ml**
Total	51	100%	

The above table shows that when the interval between two cardioplegias is prolonged, there is increased troponin-T release.

Lichtenstein et al, has used these two parameters in his study, to assess the efficacy of intermittent warm blood cardioplegia.

LTOC- Longest Time Off Cardioplegia (Longest single ischemic time in a patient)

PTCO- Percentage Time Off Cardioplegia[25]

CPB DURATION:

Average CPB duration: **97 ± 2 minutes**

Maximum : 140 minutes

Minimum : 57 minutes

CPB duration	Number of patients	%	Average Troponin-T value for this group
≤97 minutes	21	41.1%	**0.658 ng/ml**
>97 minutes	30	58.8%	**0.709 ng/ml**
total	51	100	

The above table shows that when CPB duration is increased, Troponin-T levels are elevated.

REQUIREMENT OF INOTROPIC SUPPORTS:

Inotropic support	Number of patients	%	Average Troponin-T value for this group
Nil	15	29.4	**0.522 ng/ml**
Minimal / Intermediate	30	58.8	**0.729 ng/ml**
High	6	11.8	**0.894 ng/ml**
Total	51	100	

From the above table, it is evident that higher doses of inotropes are required in those patients whose Troponin- T values are high.

DURATION OF INOTROPIC AGENTS:

37 (72.5 %) patients required inotropic for ≤ 2 days. Their average Troponin-T value was: **0.59 ng/ml**.

14 (27.5) patients required inotropic support for more than 2 days. Their average Troponin-T value was: **0.93 ng/ml.**

Duration of inotropic support	Number of patients	%	Average Troponin-T value for this group
≤ 2days	37	72.5%	**0.59 ng/ml**
> 2 days	14	27.5%	**0.93 ng/ml**
Total	51	100	

DURATION OF VENTILATION:

44 (86.3%) patients required ventilation for less than 24 hours and their average Troponin-T value was: **0.61 ng/ml.**

7 (13.7%) patients required ventilation for more than 24 hours and their average Troponin-T value was: **1.17 ng/ml.**

Duration of ventilator support	Number of patients	%	Average Troponin-T value for this group
Less than 24 hours	44	86.3%	**0.61 ng/ml**
More than 24 hours	7	13.7%	**1.17 ng/ml**
Total			

RELATIONSHIP BETWEEN DC SHOCK AND TROPONIN-T VALUES:

9 patients received DC shock after cross clamp release for defibrillation. For those patients who received DC shocks, the average Troponin-T value was: **0.85 ng/ml**. [Minimum: 0.32 and Maximum: 1.90]

42 patients did not receive DC shock. For those who did not require DC shocks, the average Troponin-T value was: **0.65 ng/ml** [Minimum: 0.12 and Maximum: 1.88]

This data suggests that DC shock may be a cause for Troponin-T elevation.

REQUIREMENT OF IABP:

Only one patient required IABP support in the postoperative period and her Troponin-T value was 0.517 ng/ml.

POST-OPERATIVE EVIDENCE OF FAILURE:

Postop cardiac failure	Number	%	Average troponin-T value for this group
No	40	78.4	**0.607 ng/ml**
Yes	11	21.6	**0.981 ng/ml**
Total	51	100	

40 patients had no evidence of cardiac ischemia/failure (ECG/ECHO/clinical) postoperatively and their average Troponin-T value was **0.607 ng/ml.**

11 patients had evidence of cardiac failure (ECG/ECHO/clinical) postoperatively and their average Troponin-T value was **0.981 ng/ml.**

ICU STAY:

28 (54.9 %) patients had ICU stay of ≤ 5 days. Their average Troponin-T value was **0.655** ng/ml.

23 (45.1 %) patients had ICU stay of > 5 days. Their average Troponin-T value was **0.727** ng/ml.

Mean ICU stay – 5.29 days

Median ICU stay – 5 days

(The average duration of ICU stay is notably high because it is our hospital policy to retain the patients in ICU for an average of 5 days)

ICU stay	Number of patients	%	Average Troponin-T level for this group
≤ 5 days	28	54.9%	**0.655 ng/ml**
> 5 days	23	45.1%	**0.727 ng/ml**
Total	51	100	

TOTAL HOSPITAL STAY AFTER SURGERY:

24 (48.8 %) patients (excluding 2 deaths) had ≤ 12 days of hospital stay.

25 (51.2 %) patients had > 12 days of hospital stay.

For patients who had less than 12 days of hospital stay, the average Troponin-T value was: **0.51ng/ml .**

For patients, who had more than 12 days of hospital stay, average Troponin-T value was: **0.82 ng/ml.**

Total hospital stay after surgery	**Number of patients**	**%**	**Average Troponin-T level for this group**
≤ 12 days	24	48.8%	**0.510 ng/ml**
> 12 days	25	52.2%	**0.820 ng/ml**
Total	49		

NYHA STATUS:

Pre-op NYHA	Frequency	Percent
II	5	9.8
III	38	74.5
IV	8	15.7
Total	51	100.0

Post-op NYHA	Frequency	Percent
I	17	33.3
II	25	49.0
III	7	13.7
IV	2	3.9
Total	51	100.0

Postoperatively, 42 patients were in NYHA I/II. Their mean Troponin T value was **0.57** ng/ml

7 patients were in NYHA III/IV. Their mean Troponin T value was **1.26** ng/ml.

NYHA (Post- OP)	**Frequency**	**Percent**	**Average Troponin-T for this group**
I&II	42	82.3%	**0.57 ng/ml**
III&IV	9	17.6%	**1.26 ng/ml**
	51	100%	

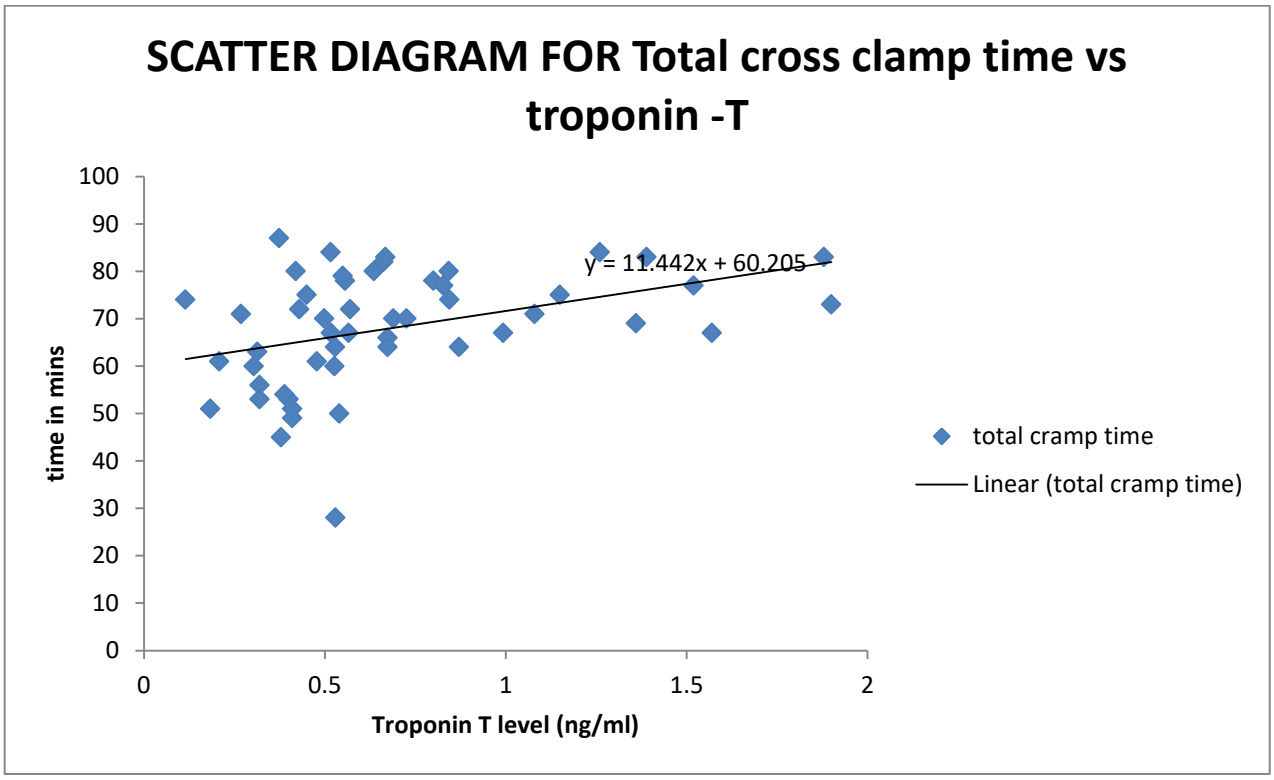
This table shows that when Troponin-T level is high, the patient is more likely to be in NYHA Class III or VI.

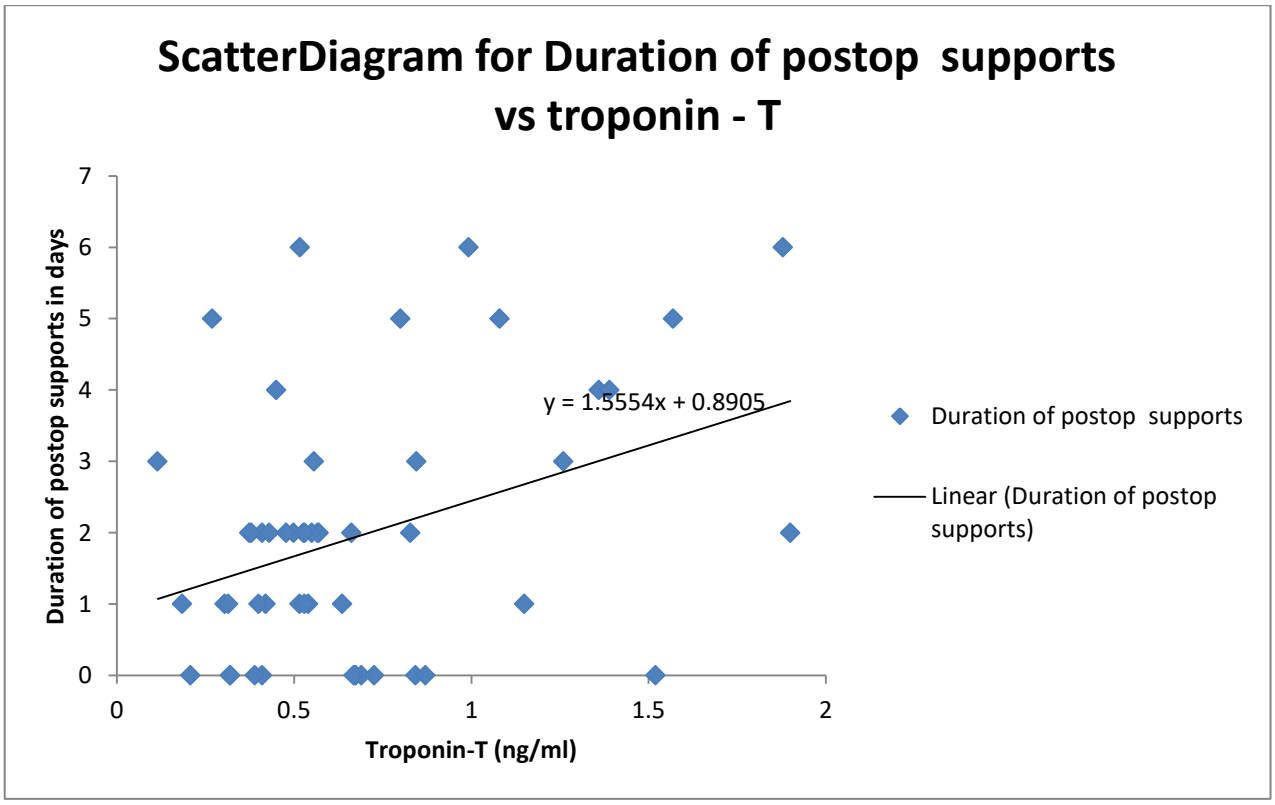
MORTALITY:

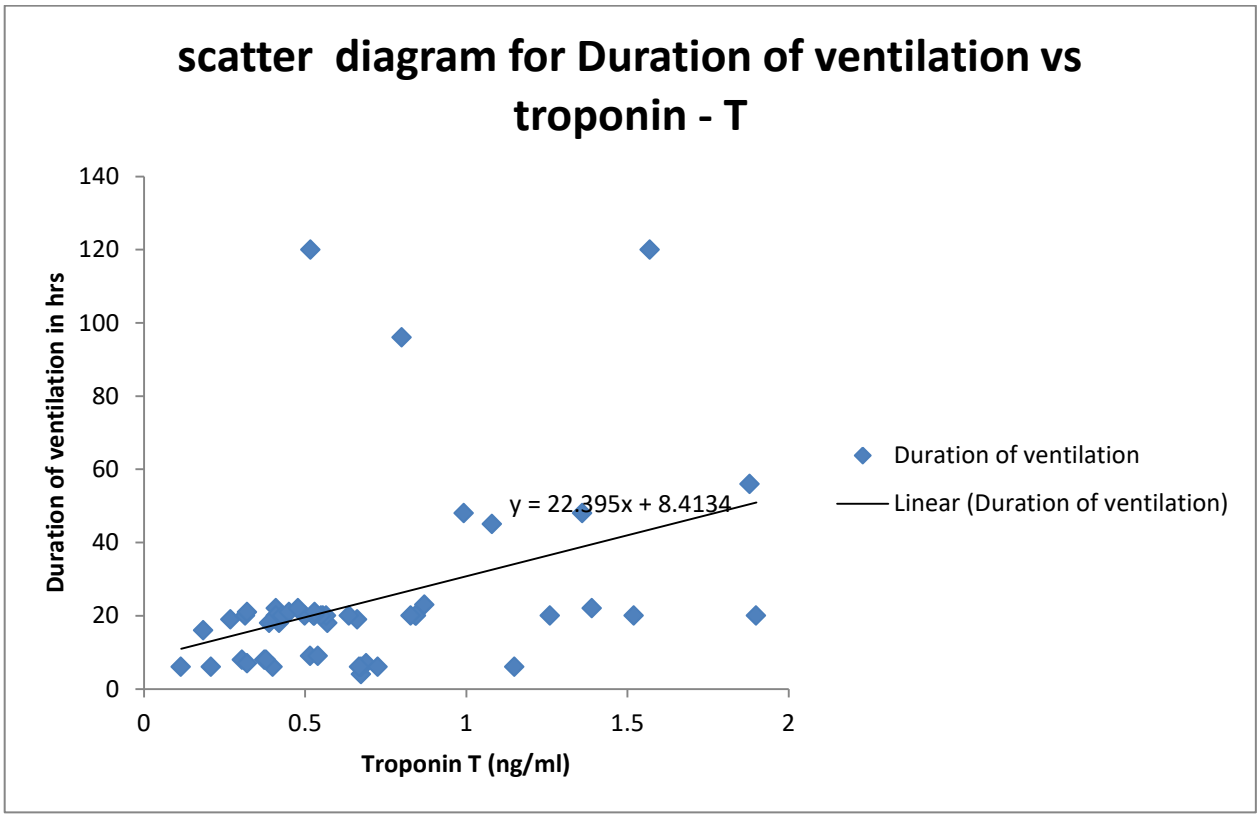
Only two patients died in our study population. Their Troponin-T values were 1.570 and 0.80 ng/ml.

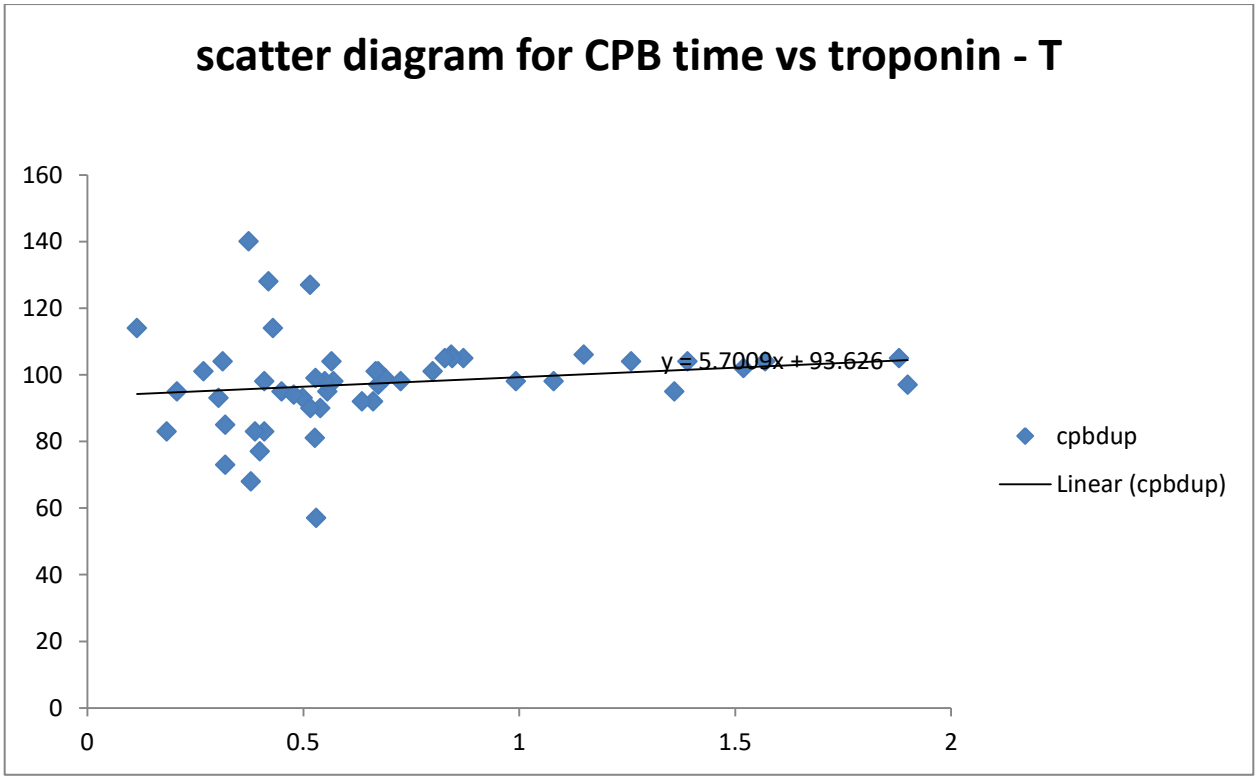
DESCRIPTIVE STATISTICS FOR THE VARIABLES:

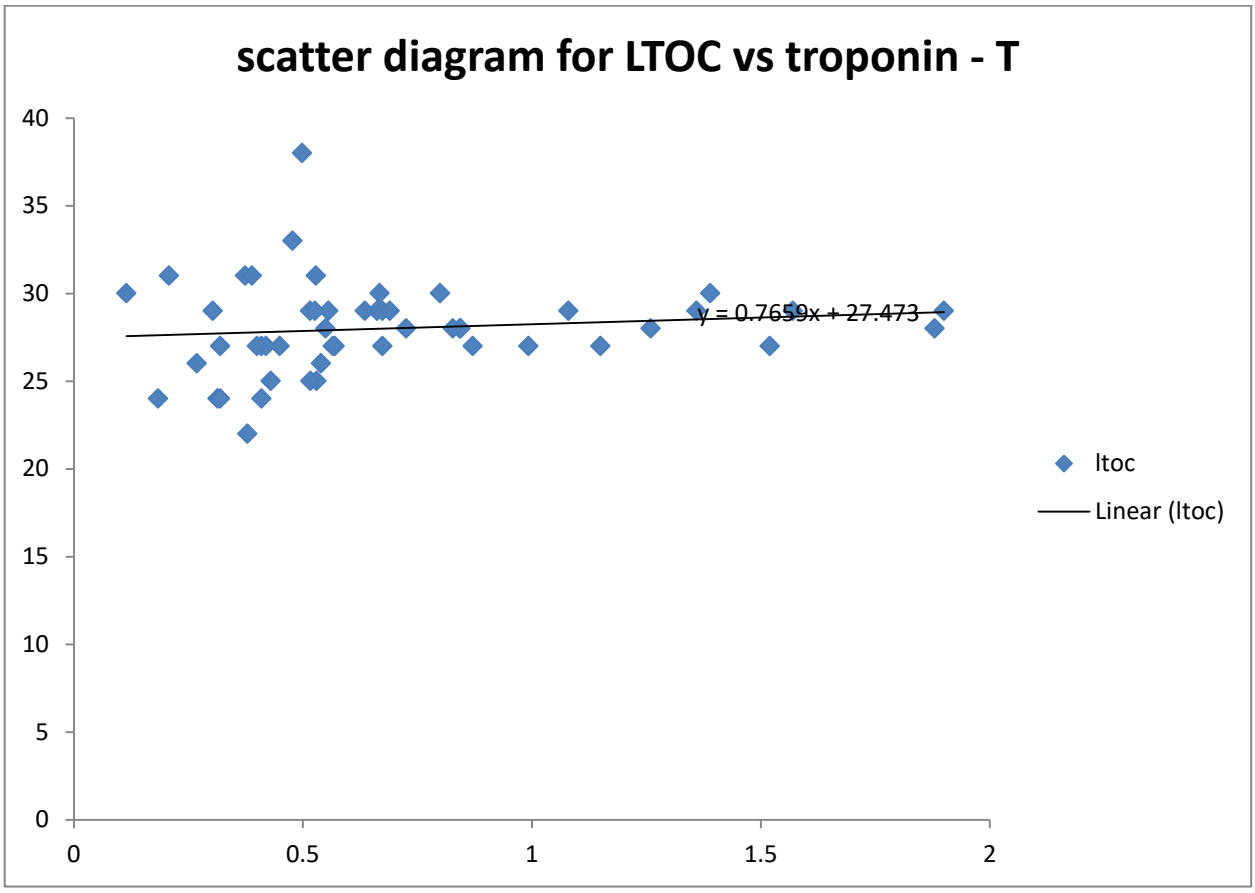
	N	Minimum	Maximum	Mean	Std. Deviation
Age	51	15	61	32.92	12.020
Sex	51	1	2	1.75	.440
Troponin T	51	.12	1.90	.6881	.41895
Cross_cramp_time	51	28.00	87.00	68.0784	12.17020
Cpb duration	51	57.00	140.00	97.5490	13.89146
LTOC	51	22.00	38.00	28.0000	2.59230
ATOC	51	21.00	34.00	25.9804	2.59608
No_of_CPs	51	1.00	4.00	2.4118	.60585
Duration_of_postop__supports	51	.00	6.00	1.9608	1.79956
Duration_of_ventilation	51	4.00	120.00	23.8235	24.98536
Postop_EF	51	40.00	84.00	62.9216	14.17581
ICU_stay	51	3.00	12.00	5.2941	2.44372
Total_hospital_stay_after_surgery	51	7.00	30.00	12.7843	4.80963

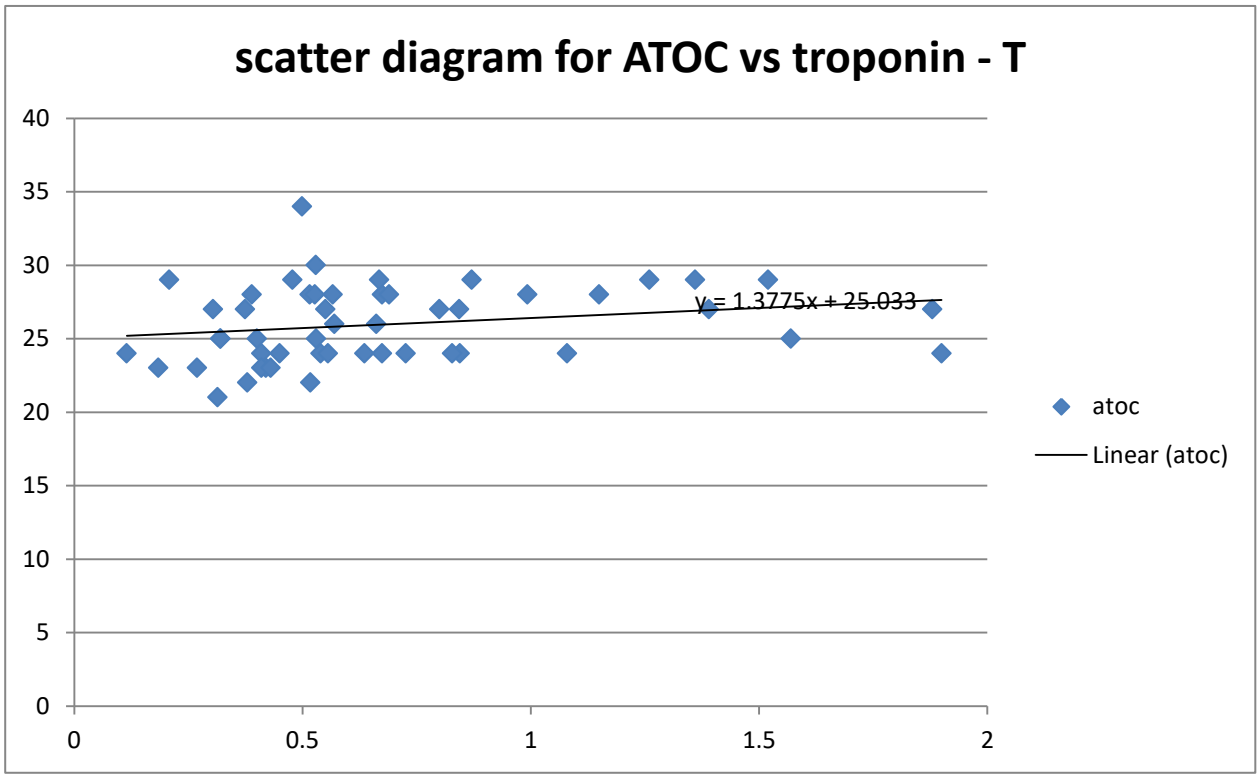

SCATTER DIAGRAM FOR Total cross clamp time vs troponin -T
time in mins
Troponin T level (ng/ml)
y = 11.442x + 60.205
total cramp time
Linear (total cramp time)

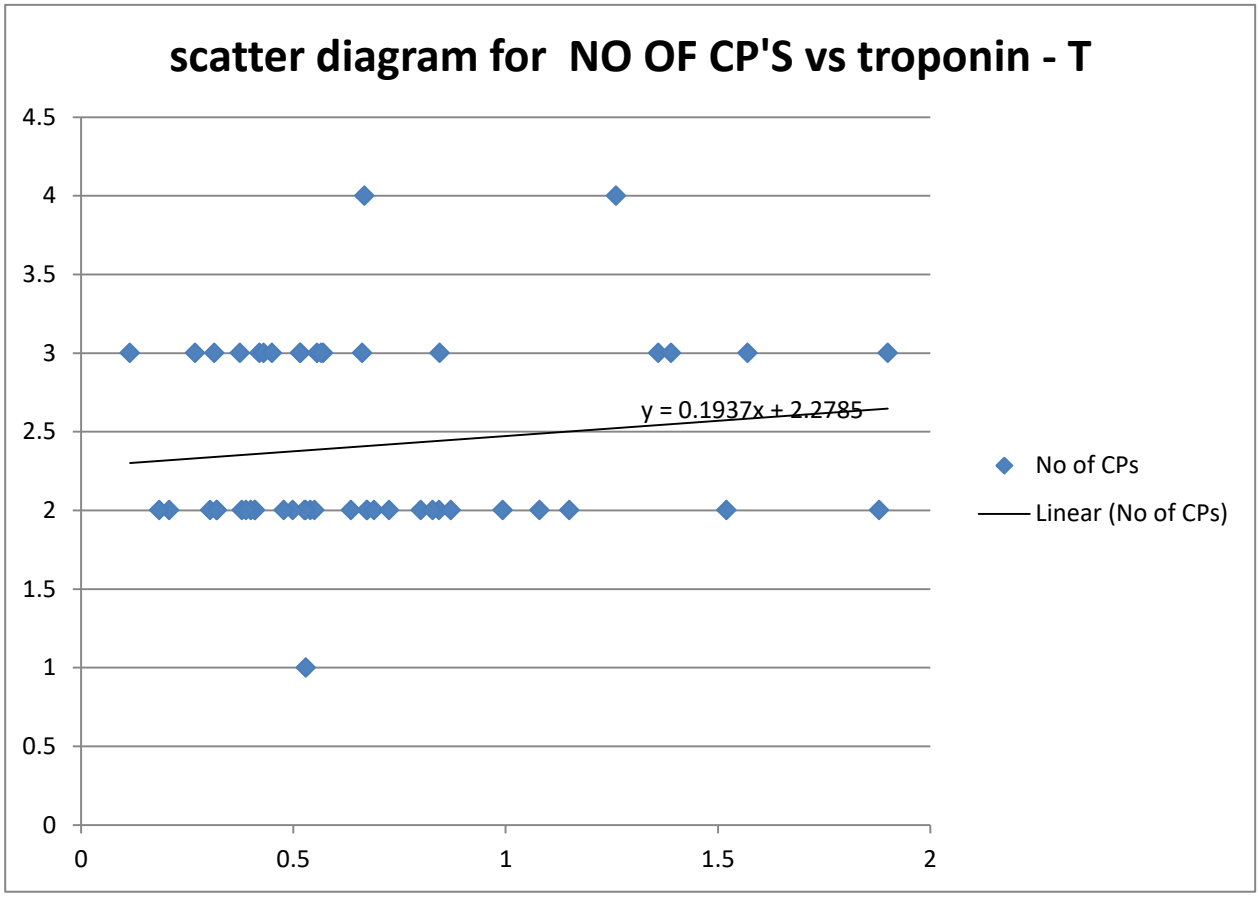

ScatterDiagram for Duration of postop supports vs troponin - T
Duration of postop supports in days
Troponin-T (ng/ml)
y = 1.5554x + 0.8905
Duration of postop supports
Linear (Duration of postop supports)


scatter diagram for Duration of ventilation vs troponin - T
Duration of ventilation in hrs
140
120
100
80
60
40
20
0
0
0.5
1
1.5
2
Troponin T (ng/ml)
y = 22.395x + 8.4134
Duration of ventilation
Linear (Duration of ventilation)


scatter diagram for CPB time vs troponin - T
160
140
120
100
80
60
40
20
0
0
0.5
1
1.5
2
y = 5.7009x + 93.626
cpbdup
Linear (cpbdup)


scatter diagram for LTOC vs troponin - T
y = 0.7659x + 27.473
ltoc
Linear (ltoc)
0
5
10
15
20
25
30
35
40
0
0.5
1
1.5
2


scatter diagram for ATOC vs troponin - T
y = 1.3775x + 25.033
atoc
Linear (atoc)
0
5
10
15
20
25
30
35
40
0
0.5
1
1.5
2


scatter diagram for NO OF CP'S vs troponin - T
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
0.5
1
1.5
2
y = 0.1937x + 2.2785
No of CPs
Linear (No of CPs)

DESCRIPTIVE STATISTICS FOR THE VARIABLES

Troponin-T level correlation	Pearson correlation	Significance (2-tailed)	Total number
Total cross clamp time	**0.394**	**0.004**	51
CPB duration	0.172	0.228	51
LTOC	0.124	0.387	51
ATOC	0.222	0.117	51
Number of CP	0.134	0.349	51
Postop supports	0.263	0.062	51
Duration of postop supports	**0.362**	**0.009**	51
Duration of ventilation	**0.376**	**0.007**	51
Requirement of IABP	-0.06	0.684	51
ECG/ECHO evidence of ischemia	**0.429**	**0.002**	51
Clinical evidence of cardiac failure	**0.400**	**0.004**	51
Post op Ejection Fraction	**0.605**	**0.001**	51
ICU stay	0.033	0.818	51
Total hospital stay after surgery	0.142	0.319	51
mortality	0.242	0.087	51

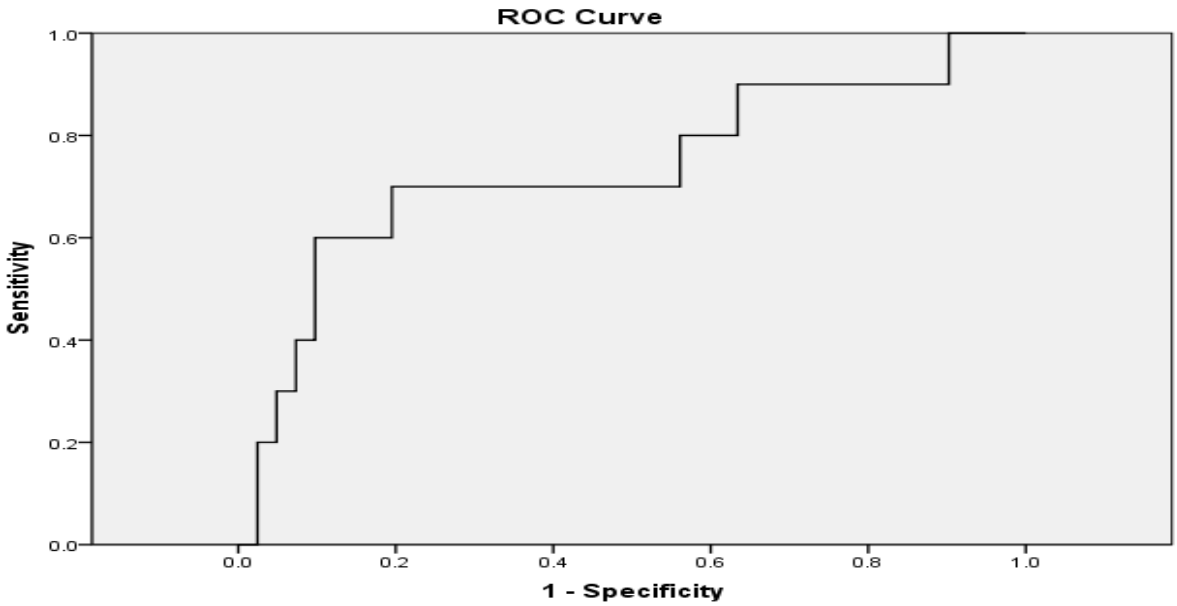
Significant at <0.05

From the above table, it can be seen that the Troponin-T level has significant correlation with the following variables:

1. Total cross clamp time (p value 0.004)
2. Duration of postoperative supports (p value 0.009)
3. Duration of ventilation (p value 0.007)
4. ECG/ECHO evidence of ischemia (p value 0.002)
5. Clinical evidence of cardiac failure (p value 0.004)
6. Postoperative Ejection Fraction (p value 0.001)

ROC (RECEIVER – OPERATOR - CHARACTERISTIC) CURVE

Post op_failure	Number
YES	11
NO	40

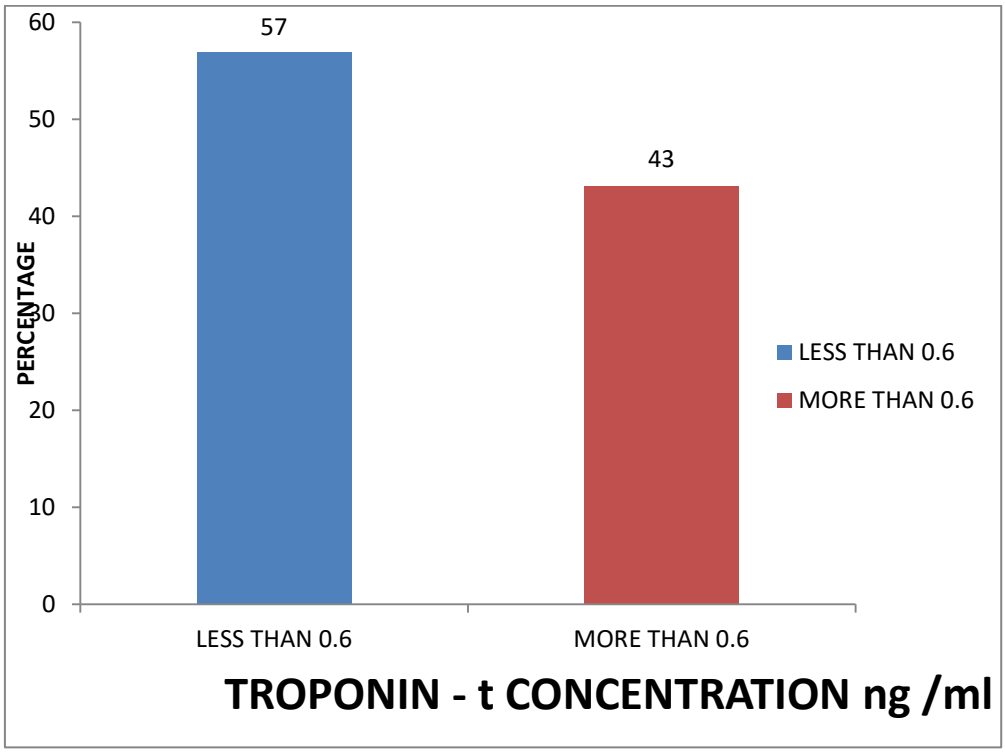


Test Result Variable(s): TroponinT

Area
.734

Based on the above ROC curve for post operative complications and troponin T levels, the optimum cut off level for troponin T is **0.6 ng/ml** (Area under the curve is 73.4%)

INDEPENDENT T-Test (Test of significance between two groups)



GROUP STATISTICS

	Troponin value	N	Mean	Std. Deviation	Std. Error Mean
	less than 0.6	29	.4163	.12311	.02286
	above 0.6	22	1.0464	.40156	.08561

	Levene's Test for Equality of Variances					
	F	Sig.	T	Sig. (2-tailed)	95% Confidence Interval of the Difference	
					Upper	Lower
TroponinT	32.817	.000	7.991	**.00006***	.78846	.47157

*significant at 0.05 level

ASSOCIATION BETWEEN CHARACTERISTIC VARIABLES AND TROPONIN T VALUE:

S. No	Variables	Troponin T (ng/ml)		Total	Chi-square value	P value
		≤ 0.6	**> 0.6**			
1.	**Total cross clamp time**					
	< 70	8	19	27	4.268	**0.039***
	> 70	14	10	24		
2.	**CPB time**					
	< 90	9	0	9	8.291	**0.004***
	> 90	20	22	42		
3.	**LTOC**					
	< 25	5	0	5	4.205	**0.040***
	> 25	24	22	46		
4.	**ATOC**					
	< 25	13	7	19	0.888	0.346

	> 25	16	15	31		
5.	**NO. of CP**					
	< 2	17	14	31	0.132	0.716
	> 2	12	8	20		
6.	**Post OP support**					
	Nil	6	9	15	9.009	**0.011***
	Minimal/Intermediate	22	8	30		
	High	1	5	6		
7.	**Duration of post OP support**					
	< 2 days	23	14	37	0.002	0.964
	> 2 days	6	8	14		
8.	**Requirement of IABP**					
	No	28	22	50	0.774	0.379
	Yes	1	0	1		
9.	**Post OP failure**					
	No	25	15	40	3.659	0.056*
	Yes	4	7	11		
10.	**Post OP EF score**					
	< 50 %	12	0	12	11.905	**0.001***
	> 50 %	17	22	39		
11.	**Mortality**					
	No	29	20	49	2.744	0.098
	Yes	0	2	2		

*. The Chi-square statistic is significant at the 0.05 level

From the above table, the following impressions are obtained.

1. The duration of cross clamp time has significant positive correlation with Troponin-T levels (p value 0.039)
2. The duration of CPB also has significant positive correlation with Troponin-T (p value 0.004)
3. Longest Time Off Cardioplegia has significant correlation with elevation of Troponin-T (p value 0.040)
4. High Troponin-T levels has significant correlation with Requirement of high doses of inotropes (p value 0.011)
5. High Troponin-T levels are associated with reduced Ejection Fraction in the postoperative period (P value 0.001)

LIMITATIONS OF THE STUDY:

1. Total number patients studied is less.
2. It is not a randomized controlled study.
3. Patients were operated by different surgeons and different surgical units. Different surgical units may have different approach in postoperative management, for example, early extubation versus late extubation, inotropic supports initiation and weaning, etc.,
4. Two patients had trans-septal approach (through right atrium) for mitral valve replacement. These two patients had De Vega annuloplasty in addition to MVR. Their Troponin-T values were 1.390 and 1.080 ng/ml. In this surgical approach, an additional incision is made in the inter-atrial septum. The cause for highly elevated values may be due to two incisions (right atrium and septum) and may

also be due to excessive retraction or due to the additional procedure (De Vega annuloplasty).

5. One patient had two incisions in the heart. MVR was done through left arial incision. Right atrium was then opened to perform De Vega annuloplasty. This patient's Troponin-T was 0.566 ng/ml.
6. One patient had prolonged hospital stay (30 days) and her Troponin-T value was 0.871 ng/ml. But the reason for her prolonged hospital stay was due to sternotomy wound infection. This is a confounding factor in the variable.
7. One patient had failed PTMC and subsequently taken up for surgery. It is not known whether PTMC causes elevation of Troponin-T, but MVR surgery was done only after 1 month. Hence, the previously attempted PTMC is unlikely to influence the results of Troponin-T values. Her Troponin-T value was 0.430 ng/ml.
8. One patient died on 5^{th} post-operative day. Postoperative echo showed moderate to severe aortic regurgitation (preoperative echo showed only mild AR). This may be due to unmasking of AR by improved hemodynamics after MVR surgery. The patient's Troponin-T value was 1.570 ng/ml.
9. Two patients had adherent left atrial clot. They underwent clot removal and left atrial exclusion done by internal circumferential sutures with 4-0 prolene. The clot removal process or LAA exclusion procedure may be additional sources of Troponin-T elevation. Their Troponin-T values were 0.668 and 0.499.
10. One patient underwent partial maze procedure for atrial fibrillation (using electrocautery). Her Troponin-T value was 0.517 ng/ml.

DISCUSSION

Though this study was done with limited number of patients, it clearly shows that prolonged cross clamp time is associated with elevated Troponin-T values and that elevated Troponin-T values are associated (significant association) with increased morbidity in the form of prolonged ventilatory support, prolonged inotropic support, requirement of high doses of inotropes, postoperative cardiac failure and poor ventricular ejection fraction.

The per-operative variables that are associated (significantly) with high levels of Troponin-T are 1. Prolonged cross clamp time (more than 70 minutes), 2. Prolonged CPB time (>90 minutes) and 3. Prolonged CP time (>25 minutes between 2 cardioplegia doses).

By ROC curve analysis, the cut-off value of Troponin-T, was derived, above which the morbidity is significantly increased. The cut-off value is 0.6 ng/ml. (In a study conducted by Bernard l. Croal et al, with 1365 patients, and published in "*Circulation*" Journal, 2006;114:1468-1475, the cut-off value derived by ROC curve analysis, was 0.46 ng/ml and it was proved that the mortality significantly increased above this value).[14]

In this study, Troponin-T levels show good correlation with aortic cross clamp time, CPB duration and prolonged CP interval as well as postoperative variables like prolonged inotropic supports, high dose inotropes, prolonged ventilation and reduced LV function (poor EF). Hence, it is clear that Troponin-T is a good tool to assess the adequacy of myocardial protection.

CONCLUSION

Troponin-T is a reliable indicator of extent of myocardial injury in cardiac surgical patients and is a good armamentarium in the pool of diagnostics in cardiothoracic surgical field.

This test should be used more often than now, in postoperative period, to assess the adequacy of myocardial protection. This will have two important implications.

1. In an individual patient, who is hemodynamically unstable in the postoperative period, this test is helpful, in defining the cause of it.
2. The efficiency of different techniques of myocardial protection may be compared with one another, based on Troponin-T levels.

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Sl No	Name of the patient	Age/sex	IP No	Date of surgery	Salient ECHO findings relevant to study	NYHA class	AF	CPB Time	LTOC	ATOC	Total cross clamp time	No of CPs	Postop supports	Duration of postop supports	DC shock/massage	Duration of ventilation	Requirement of IABP	ECG/ECHO evidence of ischemia	Postop failure	Postop EF	ICU stay	Total hospital stay after surgery	Postop NYHA	Mortality	Troponin-T	Other remarks
1	Sammandham	56/M	53992	12/9/12	MS(sev) PHT-mild	3	-	127	29	28	84	3	Minimal	1	-	9	-	-	-	60	5	12	1	-	0.516	
2	Rathinammal	55/F	32957	15/9/12	MS(S) MR(mild) PHT(sev)	3	-	93	29	27	60	2	Nil	1	-	8	-	-	+	70	6	10	2	-	0.304	Lasix infusion+
3	Anandhan	52/M	69179	20/9/12	MS(sev) PHT(mod)	2	+	90	26	24	50	2	Minimal	1	-	9	-	-	-	61	5	15	1	-	0.54	
4	Samanasamary	52/F	156810	18/9/12	MS(sev) MR(mild) PHT(mod) EF(N)	3	+	86	26	19	60	3	Minimal	3	+	20	-	-	-	46	4	9	2	-	0.556	
5	Vijayamani	34/F	37602	22/9/12	MS(sev) AR(mild) TR(sev) PHT(sev)	2	-	81	28	27	61	2	Minimal	1	-	6	-	-	-	46	4	12	2	-	1.15	
6	Selvi	33/F	76273	24/9/12	MS(sev) PHT(mod)	4	+	101	26	23	71	3	Interme diate	5	-	19	-	-	-	N	7	11	2	-	0.269	
7	Latha	18/F	35169	26/9/12	MR(sev) No PHT	4	+	96	23	18	69	4	Nil	3	-	20	-	+	+	45	4	17	3	-	1.26	RFT 89,3.7 upto 6 days; Dopamine started on 6th day; global hypokinesia
8	Valli	32/F	74932	28/9/12	MS(sev) PHT(sev)	3	-	102	26	23	71	3	high	5	-	120	-	+	+	N	5	5	4	+	1.57	LFT,RFT-N AR(mod-sev); RV dysfn+; Expired on 5th day
9	Chithra	40/F	54017	29/9/12	MS(sev) PHT(mod)	3	+	95	31	29	61	2	Nil	-	-	6	-	-	-	56	3	10	2	-	0.208	
10	Muniyappan	35/M	61323	3/10/12	MS(sev)	3	-	108	34	27	68	2	Nil	-	+	4	-	-	-	N	5	14	2	-	0.674	

					MR(mod) PHT(mod)																				
11	Paulraj	48/M	69064	4/10/12	MS(sev) PHT(sev)	3	-	116	26	25	78	3	Minimal	2	-	18	-	-	-	70	5	10	2	-	0.57	
12	Narayanan	30/M	74171	5/10/12	MS(sev) PHT(sev)	3	-	114	26	24	75	3	Interme diate	2	-	19	-	-	-	65	8	17	2	-	0.662	
13	Chinnaponnu	57/F	85795	8/10/12	MS(sev) MR(mod) PHT(sev)	3	-	107	27	26	79	3	High	4	-	48	-	-	-	64	10	20	3	-	1.36	
14	Suriya	22/F	89892	9/10/12	MR(mod) PHT(mod)	2	-	115	24	22	69	3	Minimal	2	+	20	-	-	-	70	3	13	1	-	1.9	
15	Nathiya	22/F	90015	19/10/12	MR(mod) No PHT	3	+	136	38	29	89	3	Minimal	2	+	20	-	-	-	N	5	10	1	-	0.566	Devega thro RA
16	Gayathri	15/F	89465	18/10/12	MR(mod) PHT(mild)	3	-	69	24	22	69	2	Nil	0	-	20	-	-	-	N	4	11	2	-	0.843	
17	Vasanth	17/M	88327	22/10/12	MR(sev) AR(mild) PHT(sev)	3	-	98	27	24	49	2	Nil	0	-	22	-	-	-	55	7	10	1	-	0.41	
18	Anjalai	25/F	93573	2/11/12	MR(sev) PHT(mild)	3	+	104	24	21	63	3	Minimal	1	-	20	-	-	-	N	7	10	1	-	0.314	
19	Selvi	32/F	96531	3/11/12	MR(sev) MS(mild) PHT(mod)	3	+	91	36	31	63	2	Interme diate	2	-	20	-	+	-	52	4	7	2	-	0.55	RV dysfn
20	Mangai	28/F	76758	5/11/12	MS(sev) PHT(mod)	3	+	73	27	25	56	2	Nil	0	-	7	-	-	-	N	5	11	2	-	0.32	
21	Gomathi	22/F	93536	7/11/12	MR(sev) AR(mild) PHT(mild) EF 59%	3	-	128	27	23	80	3	Minimal	1	-	18	-	-	-	56	8	12	2	-	0.42	
22	Varalakshmi	40/F	96593	23/11/12	MS(sev) MR(mild) PHT(sev)	4	-	83	24	23	51	2	Interme diate	2	-	20	-	-	-	56	3	13	2	-	0.41	
23	Pongala	22/F	89939	20/11/12	MR(sev) AR(mild) PHT(mild) EF 73%	3	-	114	25	23	72	3	Minimal	2	-	20	-	-	-	50	6	11	1	-	0.43	PTMC on 18/10/12
24	Sasikala	38/F	93541	16/11/12	MR(sev) PHT(mild)	3	-	83	24	23	51	2	Minimal	1	-	16	-	-	-	N	3	15	2	-	0.184	
25	Kumar	25/F	95311	21/11/12	MR(sev) MS(mod) PHT(mild)	3	-	95	31	30	63	2	Nil	0	-	6	-	-	-	N	6	13	1	-	0.674	
26	Rani	19/F	90170	28/11/12	MS(sev) MR(mild) PHT(sev)	3	-	106	35	33	66	2	Nil	0	-	23	-	-	-	N	5	30	2	-	0.871	Wound infection; sec suture
27	Maheswari	35/F	102940	28/11/12	MS(sev)	3	+	100	37	33	67	2	minimal	1	-	20	-	-	-	64	5	10	2	-	0.636	Atrial flutter+

					MR(mild) PHT(mod) EF 65%																				
28	Munusamy	18/M	97879	1/12/12	MR(mod) MS(mod) PHT(mod) EF 76%	3	-	105	31	28	60	2	Nil	0	-	7	-	-	-	N	5	14	2	-	0.69	
29	Gomathi	25/F	108855	3/12/12	MS(sev) PHT(mod) EF-N	3	-	99	31	30	64	2	Minimal	1	-	20	-	-	-	47	3	12	2	-	0.529	
30	Elavarasan	17/M	107053	4/12/12	MR(sev) TR(sev) EF 70%	4	-	123	30	27	82	3	Interme diate	4	-	22	-	-	+	60	6	15	2	-	1.39	RA approach; De Vega+
31	Sivagami	36/F	113923	12/12/12	MR(sev) PHT(mild) EF 69%	3	+	114	30	24	74	3	Minimal	3	-	6	-	+	-	43	6	14	2	-	0.115	Mod LV dysfunction
32	Rubavathi	61/F	83761	14/12/12	MS(sev) MR(mild) PHT(sev)	3	-	116	34	29	89	3	Interme diate	3	-	20	-	-	-	N	7	12	2	-	0.845	
33	Amudha	30/F	113826	13/12/12	MS(sev) MR(mod) PHT(sev) EF 62%	3	-	83	41	34	71	2	Nil	0	-	6	-	-	-	N	4	14	1	-	0.726	
34	Palaniyammal	35/F	94824	7/12/12	MS(sev) TR(sev) PHT(sev) AR(mild) EF-N	4	-	107	30	27	61	2	Interme diate	5	+	45	-	-	+	56	7	15	3	-	1.08	RAappr DeVega+ Readmission+
35	Ravikumar	27/M	115533	12/12/12	MS(sev) PHT(sev)	3	+	141	32	24	10 0	4	Nil	0	+	6	-	-	-	N	3	16	1	-	0.668	Organised LA clot
36	Devi	28/F	113844	22/12/12	MS(sev) MR(mod) PHT(mod)	2	-	77	27	25	53	2	Minimal	1	-	6	-	-	-	N	5	10	1	-	0.4	
37	Dinesh	15/M	7849	5/2/13	MR(sev) No PHT EF 67%	3	-	76	26	22	48	2	Nil	0	+	20	-	-	-	56	3	14	1	-	1.52	
38	Sasikala	30/F	2006	5/2/13	MR(sev) MS(mild) PHT(mild) EF 60%	3	+	81	29	28	60	2	Minimal	2	-	20	-	-	-	54	3	8	1	-	0.527	
39	Mohankumar	38/M	4599	4/2/13	MS(sev) PHT(mild)	2	-	140	31	27	87	3	Minimal	2	-	8	-	-	-	51	3	14	1	-	0.374	
40	Chellathayee	50/F	5324	2/2/13	MS(sev) MR(mild) PHT(mild)	3	+	76	26	22	47	2	High	5	-	96	-	+	+	40	9	9	4	+	0.8	Reex-0 pod for bleed Renal fail; exp

																									on 9th pod
41	Sangothai	49/F	118764	15/1/12	MS(sev) MR(mild) PHT(sev) LA clot	3	-	93	38	34	70	2	Minimal	2	-	20	-	-	-	N	7	9	2	-	0.499	Clot removal LAA exclusion by prolene
42	Vijayalakshmi	30/F	116197	4/1/13	MS(sev) MR(mod) PHT(sev) AR(mild) EF-N	4	+	82	32	30	64	2	Minimal	2	-	20	-	-	-	52	8	13	2	-	0.828	
43	Rani	42/F	123792	1/2/13	MS(sev) PHT(sev)	3	-	102	36	35	76	2	High	6	-	48	-	+	+	N	12	18	3		0.993	Septal hypokinesia+
44	Chinnapillai	35/M	115845	9/1/13	MR(sev) AR(mild) No PHT	3	-	68	22	22	45	2	Minimal	2	-	8	-	-	-	58	6	15	2	-	0.379	
45	Divya	17/F	12273	26/2/13	MR(mod-sev) MS(mild) PHT(mod) EF-N	3	-	85	24	25	53	2	Nil	0	+	21	-	-	-	N	5	10	1	-	0.32	
46	Gnanasoudari	29/F	121908	26/2/13	MS(sev) PHT(mild) EF-N	3	+	95	27	24	75	3	Interme diate	4	-	21	-	-	+	N	6	12	2	-	0.45	
47	Pothumani	29/F	16686	28/2/13	MS(sev) MR(mod) AR(mild) AS(mild) PHT(mild)	3	-	57	25	25	28	1	Minimal	2	-	21	-	-	-	N	4	10	3	-	0.53	
48	Kamala	35/F	13942	27/2/13	MS(sev) MR(mild) PHT(mild)	4	-	83	31	28	54	2	Nil	0	+	18	-	-	-	N	5	14	1	-	0.389	
49	Seetha	22/F	6186	1/3/13	MS(sev) PHT(mod) AR(mild) EF-N	3	-	82	29	27	60	2	High	6	-	56	-	+	+	56	10	18	3	-	1.88	Re-intubation+; RV dysfn; Paradox septal motion
50	Rajeshwari	35/F	16317	6/3/13	MS(sev) MR(mild) PHT(mild)	3	-	94	33	29	61	2	Interme diate	2	-	22	-	-	-	58	3	17	1	-	0.478	
51	Amsaveni	42/M	14138	2/3/13	MR(sev) MS(mild) PHT(mod) EF 55%	4	+	90	25	22	67	3	High	6	-	120	+	-	+	57	12	25	3	-	0.517	Partial maze done; IABP 2nd-4th days

INFORMEDCONSENTFORM

Title of the study: Postoperative Troponin-T as a Marker of Myocardial Ischemic Injury in Mitral Valve Replacement Surgeries

Name of the Participant: _____

Name of the Principal Investigator: Dr. N. Jothilingam

Name of the Institution: Rajiv Gandhi Government General Hospital & Madras Medical College, Chennai-3

I _____have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "**Postoperative Troponin-T as a Marker of Myocardial Ischemic Injury in Mitral Valve Replacement Surgeries"**.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained that **2ml of blood will be collected from me 24 hours after the surgery.**
5. I have been explained about my rights and responsibilities by the investigator.
6. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
7. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****
8. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
9. I have understood that my identity will be kept confidential if my data are publicly presented.
10. I have had my questions answered to my satisfaction.
11. I have decided to be in the research study.
12. I have the right to refuse to give blood sample in case I don't want to, for any reason.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For Adult Participants:

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____Signature_____Date_____

Name and Signature of impartial witness (for illiterate patients):

Name _____Signature_____Date_____

Address and contact number of the impartial witness:

_____

Name and Signature of the investigator or his representative obtaining consent:

Name _____Signature_____Date_____

For Children being enrolled in research:

Whether child's assent was asked: Yes / No (Tick one)
[If the answer to be above question is yes, write the following phrase: You agree with the manner in which assent was asked for from your child and given by your child. You agree to have your child take part in this study].
[If answer to the above question is'No', give reason (s) :_____.

Although your child did not or could not give his or her assent, you agree to your child's participation in this study.

Name and Signature of / thumb impression of the participant's parent(s) (or legal representative)

Name _____
Signature _____
Date _____

Name _____
Signature _____
Date _____

Name and Signature of impartial witness (required for parents of participant child illiterate):

Name _____
Signature _____
Date _____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent :

Name _____
Signature _____
Date _____

Signature of the principal investigator with date:

INTRODUCTION

Cardiac surgery is often complicated by some degree of myocardial ischemic damage, despite much improvement in myocardial protection strategies and surgical techniques. But, precise markers that can easily and specifically identify and quantify the extent of such damage is lacking. Electrocardiographic changes are of limited value in the perioperative period. Trans-esophageal echocardiography may be helpful in assessing left ventricular function and regional wall motion (which are indirect indicators of adequacy of myocardial protection) but it lacks the sensitivity to detect subtle degrees of myocardial damage. But, it is very essential to identify perioperative myocardial injury and its extent because it directly affects postoperative outcome. Further, the assessment of such injury is helpful to compare different methods of myocardial protection and will be useful in perioperative management of patients.

The development and availability of Troponin assays are considered to be one of the most important innovations in the past decade in cardiac diagnostics. Cardiac troponins (Troponin-T and Troponin-I) are proteins that are present in the thin filaments of myofibrils. They are released into the circulation whenever there is myocardial damage. Cardiac troponins are specific for cardiac muscle and are not expressed in skeletal muscle fibers. Due to their high sensitivity and specificity, they are appropriate markers for perioperative myocardial ischemic injury.

But several studies, which have plotted the kinetics of the Troponins, have shown that cardiac surgery *per se*, causes elevation of Troponin levels in the blood even when there is no evidence of myocardial ischemic damage. This is because of surgical trauma to the myocardium. The level of increase varies with different types of surgeries and with different lengths of incisions. It is difficult to define a cut-off value for Troponin levels which will indicate a perioperative MI in patients who have undergone CABG, because

Troponin is universally elevated in all patients who undergo cardiac surgery. This rise is due to both surgical trauma and myocardial ischemic injury. Thus, the significance of Troponin levels in post-cardiac surgery patients is still ill-defined.

However, we hypothesized that if high Troponin levels result in poor postoperative outcomes (e.g. increased duration of ventilation, duration of ICU stay, duration of inotropic requirement, cardiac failure, mortality, etc.) and *vice versa*, that would indicate that Troponin is a reliable marker for extent of myocardial "ischemic" damage because pure surgical trauma alone (which is same for any single type of surgery) is not going to have any influence on these postoperative outcomes.

AIM OF THE STUDY

Our prospective study was thus designed to analyse the correlation between postoperative outcomes and Troponin-T level and to find out if there is any positive correlation between Aortic cross clamp time and Troponin-T.

If there is definite positive correlation between aortic cross clamp time and Troponin-T levels and between postoperative outcomes and Troponin-T levels, that becomes a definite evidence that this test is a viable and effective test in cardiac surgical field to assess the extent of myocardial ischemic injury.

REVIEW OF LITERATURE

HISTORY OF EVOLUTION OF THE CONCEPT OF MYOCARDIAL PROTECTION

Cardiac surgical procedures have been considered as unrealistic attempts even just 100 years back. Billroth and Paget have viewed cardiac surgery with skepticism. The first successful cardiac surgical procedure was the suturing of a stab wound in the right ventricle by Ludwig van Rehn in 1986. In 1902, Luther Hill performed a successful surgical procedure for a case of cardiac tamponade. These procedures, seemingly simple now, were performed one hundred years back as emergency resuscitative measures when cardiac surgery was unknown.

Frederick Trendelenburg performed experimental pulmonary embolectomy in animals using "inflow occlusion" technique. Kirschner, a student of Trendelenburg, performed a successful pulmonary embolectomy in a human in 1924 using the same inflow occlusion technique. The need for myocardial protection was not known at that time. The inflow occlusion was used just to get a bloodless field.

Alexis Carrel performed a descending aorta to coronary artery anastomosis in 1910 in a dog. He was able to finish this anastomosis within 3 minutes of interruption of circulation. But, the fact that the heart fibrillated within these 3 minutes and the dog subsequently died after 2 hours, made him conclude that the anastomosis should be completed within 3 minutes and this important observation led to the knowledge that the heart cannot withstand ischemia under fibrillating conditions.

Gibbon developed a cardiopulmonary bypass machine and started doing surgeries for congenital heart diseases in children. Due to repeated failures, he subsequently stopped using the machine.

Lillehei, using cross circulation, proved that heart surgeries could be feasible. CPB technology helped him perform successful surgeries and hence abandoned cross circulation after using it in 45 patients from 1954 to 1955.

During the next few decades, the concept of global organ protection evolved with the use of hypothermia. In 1961, Hufnagel and colleagues introduced the concept of myocardial cooling by ice slush.

Gradually, more complex cardiac surgeries were attempted. These procedures obviously needed longer periods of ischemia. Hence all these hearts suffered greater ischemic damage which was a great concern. Hypothermia was used to protect the heart from severe ischemic injury by lowering basal metabolic rate. But it did not provide a satisfactory protection for the heart. The concept of aortic cross-clamping was then applied. The heart stopped beating because of deprivation of high energy phosphate stores due to absence of blood supply. The cross-clamping technique greatly facilitated the surgery but at the same time making the heart prone to greater ischemic injury.

At this time, Melrose described that the heart could be arrested by chemical technique rather than by ischemic technique. He used potassium citrate to chemically arrest the heart and postulated that this preserves high energy phosphates in the heart and hence it is safe. But contrary to his expectations, this technique did not provide adequate myocardial protection and was in fact abandoned in many centers. Topical hypothermia was then added as an adjunct to this form of cardioplegia for better cardiac protection. In St. Thomas Hospital in London, Hearse et al. developed a solution, which provided reliable cardiac arrest and good myocardial protection.[1]

Gay and Ebert refined cardioplegia formulations in 1970s and 1980s. Follett and Buckberg described various strategies of cardioplegia delivery (temperature of cardioplegia solution, various routes of administration, etc). Buckberg found that blood was very useful

as a medium for cardioplegia administration. The composition of cardioplegic solutions continue to be modified worldwide according to various study reports proving superiority of one over another.

In 1978, Buckberg showed the importance of use of hyperkalemic reperfusate initially before aortic cross clamp is released.[2]

DAMAGE FROM MYOCARDIAL ISCHEMIA

Functional impairment of cardiac muscle in the absence of muscle necrosis is called myocardial stunning. This is usually a reversible phenomenon though it may last for few minutes to few days.

Myocardial cell necrosis occurs when the ischemic process is prolonged though the time duration beyond which necrosis of muscle fibers starts has not yet been defined. The extent of myocardial cell necrosis is strongly influenced by various myocardial protection strategies.

Contracture develops in cardiac muscle when ATP levels become critically low. This phenomenon is demonstrable in animals but uncommon in humans probably because the time to contracture is quite long in humans. The stone heart phenomenon usually starts in basal region of left ventricle and in subendocardium.

DAMAGE FROM REPERFUSION

Reperfusion damage to the myocardium is due to uncontrolled reperfusion i.e. reperfusion by unmodified blood and without control of flow or pressure.[2]

The mechanism of reperfusion injury involves free oxygen radicals and calcium influx into myocytes.

The event of myocardial damage sustained due to ischemia cannot be separated from that due to reperfusion injury because both are interdependent. But the surgeon has the unique opportunity to control these two events separately.

As the duration of ischemia prolongs, the myocardium undergoes the stage of myocardial stunning initially, and then myocardial necrosis. If ischemic process continues, stone heart develops, which usually indicates irreversible myocardial damage. This same course of events apply to reperfusion injury also.

In any one heart, different areas of myocardium may be different stages of ischemic injury. Usually patchy areas of necrosis are interspersed among normal areas of viable myocardium.

Microscopically, both apoptosis (programmed cell death without inflammation) and cell necrosis (cell death associated with inflammation) occur in post-cardiac surgical patients. Markus Malmberg, has demonstrated in animal studies that more the cardiac ischemic time more the degree apoptosis in cardiac muscle and also that ischemic preconditioning reduces the degree of apoptosis for any given duration of ischemic time.

VULNERABILITY OF THE DISEASED HEART

Hypertrophied heart is more susceptible to ischemic and reperfusion injury than a normal sized heart.

Chronic heart failure makes the heart more vulnerable to ischemic damage due to its already energy depleted state.

SURGICAL REQUIREMENTS

Cardiac operations can be performed when the heart is beating and it is being perfused or during induced ventricular fibrillation, but a precise and complete intracardiac surgical procedure requires a quiescent heart and a bloodless field. This would also prevent systemic air embolism. Hence aortic cross clamping becomes a necessity for most cardiac operations. So, myocardial protection becomes mandatory in order to prevent ischemic myocardial damage. Cardiac activity should be immediately stopped to prevent depletion of high energy phosphate stores. This is accomplished by chemical cardiac arrest by cardioplegic solution containing potassium.

Since aortic cross clamping and cardioplegic arrest of the heart are routine procedures in open heart surgeries and during aortic cross clamping the heart is deprived of its blood supply through coronaries, various standardized myocardial strategies have evolved over time to avoid ischemic damage to the myocardium during this period of myocardial ischemia. Some of them are projected to be superior to other techniques by various studies. But cardioplegic arrest of the heart is the gold standard against which others may be compared.

CARDIOPLEGIA DELIVERY METHODS

The goal of any technique of cardioplegia administration is to have uniform distribution of the solution to entire myocardium thus ensuring good myocardial protection. However, there is no single technique that is “best” for all circumstances. A practical knowledge of all the available techniques will help in special situations where other modes of cardioplegia delivery will be more useful than the conventional one in providing optimum protection to the myocardium.

Antegrade cardioplegia:

In this technique, the cardioplegia is administered through aortic root, coronary ostia or bypass conduits after completing distal anastomosis in CABG.

Most of the centers worldwide use the antegrade technique where cardioplegia is infused through aortic root because the technique is simple and efficient. It mimics the natural way of blood flow through coronaries. This method is not suitable in cases of aortic regurgitation or dissection in which aortotomy is done and the solution is administered through coronary ostia. Lifting or retraction of the heart (e.g. in Mitral valve surgeries) distorts the aortic valve and hence the heart must be repositioned before administering cardioplegia through aortic root.

Intermittent and continuous cardioplegia:

Continuous cardioplegia provides better myocardial protection but it is difficult to have a bloodless field in this technique and it also complicates the surgical field due to additional cannulae.

Retrograde cardioplegia:

It is helpful in patients with significant coronary artery stenoses where antegrade cardioplegia alone may not result in adequate distribution to entire myocardium. In this method, cardioplegia can be administered without interrupting the conduct of surgery. It is also useful for de-airing the coronaries and aortic root.

The right ventricle and posterior aspects of the septum are not adequately perfused by cardioplegic solution in this method due to proximity of their draining veins to the coronary sinus ostium.

It is also important to limit the retrograde pressure from 25 to 35 mmHg. Pressures of more than 50 mmHg will produce myocardial edema and hemorrhage.

Combined antegrade and retrograde cardioplegia:

This method provides the opportunity to gain optimum benefits of both antegrade and retrograde cardioplegias in a single patient.

Various compositions of cardioplegia solutions:

Basically two different types of solutions are described:

1. Extracellular or St. Thomas solution type
2. Intracellular or Breschneider solution type.

Extracellular solutions contain high sodium and calcium content with added magnesium. Intracellular solutions contain low sodium and calcium concentrations. Of these two types, the extracellular type is the most commonly used cardioplegia solution worldwide though some centers still continue to use intracellular type.

Each of these subtypes has been modified in their compositions and concentrations by different manufacturers.

Crystalloid and blood cardioplegia:

Crystalloid cardioplegia is simple, cheap and easy to prepare and administer. Blood cardioplegia provides the following benefits:

1. Ability to carry oxygen
2. Excellent buffering capacity
3. Scavenges free oxygen radicals
4. Electrolyte and osmotic compositions are similar to blood

Temperature of cardioplegia solution:

Cold cardioplegia (administered at 4 degree Celsius) is believed to provide better myocardial protection than warm cardioplegia (administered at 34-35 degree Celsius) though some studies have proved both of them to be equally effective. Tepid cardioplegia (28 degree Celcius) may provide advantages of both cold and warm solutions.

Additives in cardioplegia:

Since the potassium used in the cardioplegia is injurious to coronary vascular endothelium, additives are being tried which may reduce the dose of potassium to produce cardiac arrest.

Nicorandil, an ATP sensitive potassium channel opener, is one such agent used to reduce the dose of potassium in cardioplegia solution. This drug also prevents perioperative coronary spasm. It has also been proved to precondition the heart against subsequent ischemic injury.

L-arginine acts as a nitric oxide donor and helps in preventing endothelial dysfunction in ischemia-reperfusion injury. Its addition in cardioplegia solution has been shown to reduce postoperative Troponin-T release.[1]

ADDITIONAL STRATEGIES OF MYOCARDIAL PROTECTION:

Volatile anesthetic agents:

Volatile anesthetic agents (Isoflurane, Sevoflurane) have been proved to enhance myocardial protection by poorly understood complex and multifactorial mechanisms. They ameliorate the deleterious effects of free oxygen radicals in the phase of ischemia-reperfusion. In addition, they modulate potassium dependent ATP channels and produces

preconditioning effect. It has been shown that postoperative Troponin-T release is reduced with their use in anesthesia. Postoperative left ventricular function also is improved.

Acute Normovolemic Hemodilution (ANH):

This technique helps in better myocardial protection in two ways. First, it reduces requirement of blood transfusion. Secondly, it improves the rheologic characteristics of the blood and a reduction in hematocrit results in lower viscosity. This enhances myocardial blood flow to underserved areas of the myocardium.

Neutrophil depletion:

Neutrophils are associated with reperfusion injury by its release of destructive enzymes, free oxygen radicals and other toxic substances. Neutrophil depletion, either in CPB circuit or in cardioplegia solution has been shown to improve postoperative myocardial performance. Postoperative Troponin-T is also less in these patients.

Other medications useful in myocardial protection:

Erythropoietin, N-acetylcysteine, Desferoxamine and Statins have also been proved to enhance myocardial protection in some studies.[1]

ISCHEMIC PRECONDITIONING:

It is a phenomenon in which a previous sublethal ischemia to the myocardium provides protection against subsequent ischemic insults. In a study conducted by Ghosh et al. postoperative release of Troponin-T was less in those patients in whom ischemic preconditioning was applied.

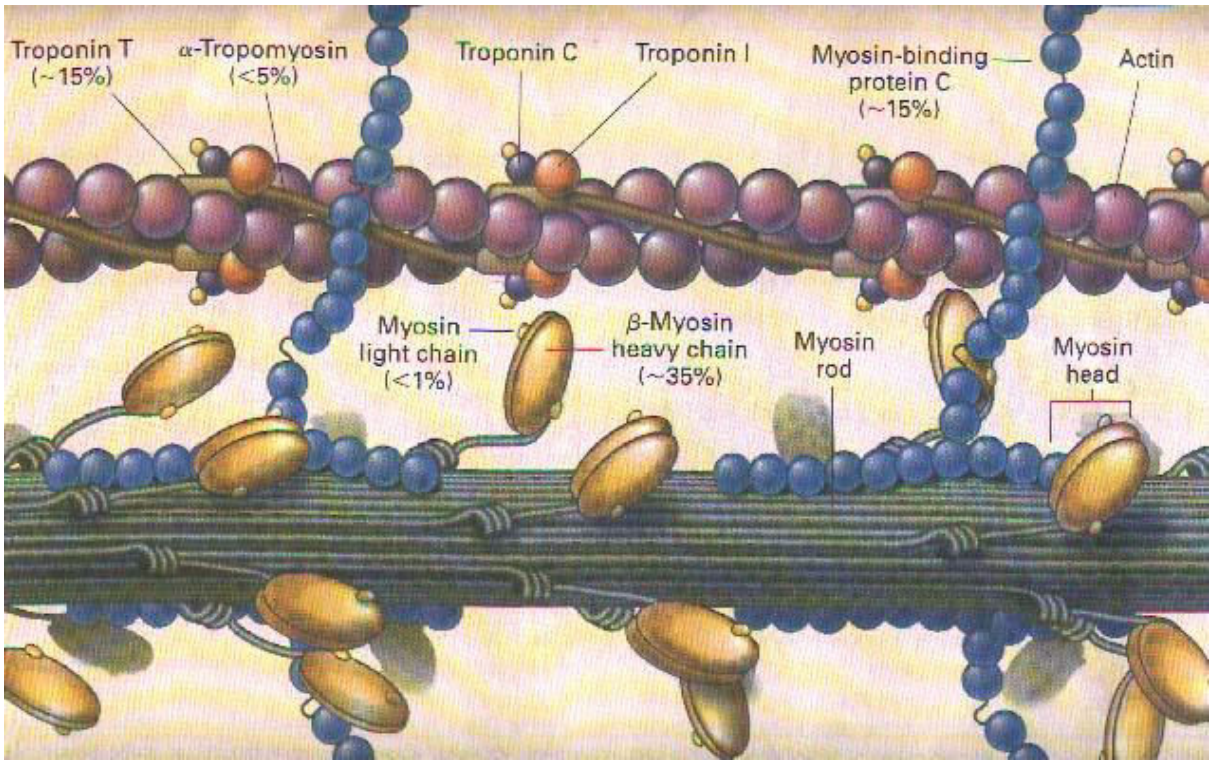
FIBRILLATION:

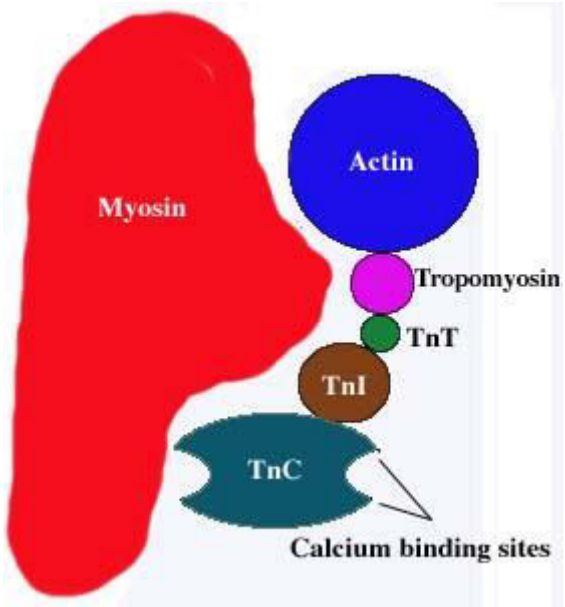
It is a useful, but less often used, strategy for myocardial protection. It relies on the principle of ischemic preconditioning. It is particularly useful in reoperative CABG surgeries where dissection and isolation of previous grafts and delivery of cardioplegia through them is difficult.

WHAT IS TROPONIN-T:

Troponin-T was discovered by Hugo A. Katus, a German physician. He subsequently developed a method to assay Troponin-T level.

The cardiac muscle is made up of myocyte composed of bundles of myofibrils which contain myofilaments. These myofibrils in turn are made up of repeating units of sarcomere. These sarcomeres are the basic contractile units of cardiac muscle. Each sarcomere is defined on either side by z lines. The sarcomere contains actin (thin filament) and myosin (thick filament). The interaction between actin and myosin and their sliding of one over another causes contraction and relaxation of cardiac muscle. Myosin has ATPase that hydrolyses ATP to provide energy for actin-myosin bridge formation. Thin filament is made up of three types of proteins: actin, troponin and tropomyosin. Actin is globular shaped protein arranged around rod shaped tropomyosin. Troponin proteins are attached to tropomyosin at regular intervals. 3 types of troponin proteins: Troponin-T, Troponin-C& Troponin-I (each coded by a separate gene). Troponin-T is attached to tropomyosin and troponin-C (which in turn is attached to Troponin-T) is the site for Calcium binding. During excitation-contraction coupling, calcium channels on sarcoplasmic reticulum open and calcium is released into sarcoplasm. These calcium ions bind to Troponin-C and bring about conformational changes in Troponin-T causing actin-myosin overlap. Troponin-I inhibits ATPase activity and thus inhibits the binding of actin and myosin and this inhibition is reversed by calcium attachment to Troponin-C.[3]





There are three tissue-specific subtypes of Troponin-T:

T1 in slow skeletal muscle fibers

T2 in cardiac muscle fibers (cTnT) and

T3 in fast skeletal muscle fibers.[4]

The clinical laboratories use assays to detect cTnT (cardiac Troponin-T). Hence, its detection is specific for cardiac origin. Specificity to cardiac origin is close to 98%. Current methods of cardiac Troponin-T assay have only 2% cross-reactivity to skeletal Troponin.

MECHANISM OF TROPONIN-T RELEASE DURING ISCHEMIC EVENTS:

Myocardial ischemic injury, either reversible or irreversible, causes increased permeability of myofibrils and thus Troponin complexes are released into circulation. Thus Troponin-T or Troponin-I assessment in blood indirectly detects myocardial ischemic damage.

Troponin is bound mainly to myofibrils (94%) and the rest 6% is cytosolic. When myocardial injury occurs, there is rapid early release of cytosolic Troponin-T and late gradual prolonged release from myofibrils. This affects the kinetics of Troponin-T release (Biphasic release pattern). The dissociation of that major portion that is compartmented in myofibrils is a time-consuming process and hence its long-lasting release. Though the serum half-life of Troponin-T is 120 minutes, this late and slow release of Troponin-T into the circulation is the reason for its values to remain high for upto 7-14 days.[5]

Myocardial depressive factors that are released in the setting of inflammatory states (e.g. sepsis, CPB) cause degradation of Troponin molecules into smaller molecules which escape into the circulation because of increased membrane permeability. [7]

ELIMINATION OF TROPONIN-T FROM BODY:

The exact mechanism of Troponin-T elimination from the body is unknown. It has been postulated that they are cleared by reticuloendothelial system (given the large size of these molecules). These large molecules are fragmented into small molecules and are

subsequently excreted by the kidney. A portion of them are also degraded by vascular endothelium.[8]

CAUSES OF ELEVATION OF TROPONIN-T IN CARDIAC SURGERY:

1. Direct surgical trauma,
2. Inadequate myocardial protection,
3. Reperfusion injury,
4. Myocardial infarction and
5. Cardioversion-defibrillation shocks

Other causes of elevations of Troponin-T [7]:

1. Acute pulmonary embolism
2. Acute pericarditis
3. Acute of severe heart failure
4. Sepsis and/or shock
5. Myocarditis
6. Hypertrophic cardiomyopathy
7. Type A aortic dissection
8. Strenuous exercise
9. Renal failure
10. Cardiac contusion after blunt chest wall trauma, external cardiac massage
11. False positive troponin- Heterophilic antibodies, Rheumatoid factor, Fibrin clots, Microparticles, Analyser malfunction

There are four different theories that explain the persistent basal elevation of Troponin-T in patients with chronic kidney disease and skeletal muscle disease.[8]

1. Theory of re-expression: in above said disease conditions, the cTnT re-expression occurs (a remembrance of early fetal form of expression)[20]
2. Theory of cross-reactivity: the skeletal form of Troponin-T cross-reacts with cTnT in the first generation assay methods. However, this is avoided in second generation assays where more specific antibodies are used.
3. Theory of isoforms: minimal amounts of isoforms of cTnT are expressed in skeletal muscles as well.
4. The kidneys have a role in clearance of Troponin-T from the body.[21]

TROPONIN-T IN CARDIAC EVALUATION:

The amino acid sequences of cardiac and skeletal forms of Troponin-T and I are different significantly and hence these two assays are useful in cardiac evaluation. But the structures of Troponin-C of both cardiac and skeletal muscle fibers are similar and so the assay of Troponin-C is not useful clinically.

ESC/ACC committee has documented that any degree of myocardial necrosis will impair the clinical course of the patient and that there is no threshold value of elevated Troponin-T below which it can be considered harmless.

It has been proved that even less than 1 gm of myocardial necrosis is detected by Troponin-T assay.[7]

SENSITIVITY OF TROPONIN-T:

Troponin-T is 95% sensitive for cardiac ischemic necrosis as it detects even subclinical levels of myocardial ischemic events (“microinfarcts”), which are not evident on ECG or ECHO findings.

SPECIFICITY OF TROPONIN-T:

With current methods of Troponin-T assay (2nd generation assays), the specificity of Troponin-T to cardiac origin is close to 98%.[11]

PATTERN OF ELEVATION OF TROPONIN-T:

Troponin-T level in blood starts to rise after 3-4 hours and peaks at 18-24 hours and lasts for 7-14 days in blood.[10]

PREVIOUS STUDY RESULTS:

Several studies have been conducted in the past in various parts of the world in similar manner as this study) to find out the significance of postoperative Troponin-T elevation.[12] Most of such studies have demonstrated positive correlation between higher Troponin-T values and increased postoperative morbidity and mortality. These studies have also derived a cut-off value for Troponin-T levels in post-cardiac surgery patients beyond which the morbidity and mortality is increased.

Most of such studies have been done on patients undergoing CABG. But, since adequacy of revascularisation and perioperative MI are major determinants of Troponin-T elevation in these kinds of patients, we didn't want to conduct a study on patients undergoing CABG surgery (because this study is aimed to find out whether Troponin-T in postoperative period reflects the inadequacy of myocardial protection). If, in this study, we had included CABG surgeries also, perioperative MI would have been a major confounding bias. Also, those patients who have evidence of significant Coronary Artery Disease were excluded from the study by conducting Coronary Angiogram in patients over 40 years of age. Those with ECG evidence of CAD were also excluded from the study.

Some other studies have been undertaken with similar intent, but by including various kinds of cardiac surgeries in a single study. Various kinds of cardiac incisions in various parts of the heart and various lengths of incisions cause various levels of elevation of Troponin-T. Atrial incisions cause lesser level of Troponin-T elevation when compared to incision on ventricular muscle. Hence, mitral valve replacement surgery (MVR) alone was taken for this study, by which we have avoided an important bias.

Sigismond Lasocki, analysed 502 consecutive patients who underwent various cardiac surgical procedures, and found that high Troponin-T value is an independent risk factor for postoperative mortality.[13]

Hugo A katus et al, performed a study on 338 patients and showed that Troponin-T improves the efficiency in diagnosis of myocardial ischemia when compared to CK-MB. (sensitivity of Troponin-T was 94% and that of CK-MB 63%)[13]

Bernard L Croal, conducted a study in 1365 patients and showed that elevated levels of Troponin-T at 24 hours after surgery was associated with increased short-term, mid-term as well as long-term mortality.[14]

James L Januzzi conducted a study on 224 patients to find out the significance of CK-MB and Troponin-T in post cardiac surgery patients. He found that elevated Troponin-T level correlated well with post operative complications whereas the correlation of CK-MB was poor.[15]

Joost Swaanenburg conducted a study on 123 patients undergoing various cardiac surgeries and found that when cross clamp time extends beyond 1 hour, there is rapid rise in Troponin-T levels. He also demonstrated that Troponin-T elevation levels depend on the type of cardiac surgery. Off-pump CABG surgeries did not cause a significant rise in Troponin-T level whereas on-pump CABG and valve surgeries produced Troponin-T elevation. Of all kinds of surgeries, valve surgeries produced highest levels of Troponin-T.[15]

H A Katus et al conducted a study in 56 patients and found that Troponin-T level raises correspondingly with cross clamp time.[16]

Russel Hirsch et al, conducted a study on 56 pediatric patients and found that Troponin-T at 1 hour after surgery indicates the extent of myocardial damage and was predictive of difficult recovery.[17]

Steven E. Lipshultz et al, conducted a study on 51 pediatric patients and showed that elevated Troponin-T levels are predictive of myocardial damage and its level correlates with increased morbidity and mortality.[18]

Luc Jacquet et al, conducted a study on 117 patients and found that Troponin-T estimation after CABG was helpful to detect perioperative ischemia or MI and was superior to ECG findings in detecting early and mild ischemia.[19]

OTHER METHODS ASSESSMENT OF ADEQUACY OF MYOCARDIAL PROTECTION:

Adequacy of myocardial protection cannot be assessed directly but can only be assessed by indirect methods like ECG, Echocardiogram and by various factors that are influenced by myocardial protection.

ECG:

Though postoperative ECG may detect a significant myocardial ischemic injury by ST-T changes, minimal global ischemic injury is not always sufficient enough to cause such changes in ECG. Patchy distribution of areas of necrosis and partially viable myocardium amidst normal areas of myocardium is common after prolonged ischemic time.

ECHO:

Regional wall motion abnormality may be detected by transthoracic ECHO (TTE) or, more accurately, by trans-oesophageal ECHO (TEE). But this finding occurs only in severely damaged myocardium. Ejection fraction in the postoperative period, when compared to preoperative status, may provide a clue to significant ischemic damage, though it may be influenced by various other factors like inotropic supports, volume status, residual anatomic lesion, patient-prosthesis mismatch, fever, sepsis, etc.

Functional status:

NYHA classification of functional status is a good tool to compare pre and postoperative status. But the classification is based on one's own subjective feeling of wellness and it is not sensitive and specific enough to detect minor or even moderate degrees of myocardial ischemic injury. A poor NYHA status postoperatively may be due to not only cardiac function impairment but also pulmonary functional status, renal function, skeletal muscle system, central nervous system, liver function, hemoglobin level, nutritional status, psychological motivation, etc.

Mortality rate:

Severe myocardial ischemic injury may be a cause of or sometimes a precipitating factor for postoperative mortality. In studies involving large number of patients, it may be found that Troponin-T elevation is a risk factor for postoperative death occurring within 1 month. But, since the mortality rates of open heart surgeries are generally very low in most of the cardiac surgical centers, the use of mortality rate, as an indicator of poor myocardial protection, is difficult in small scale studies.

CK-MB:

Since these enzymes are found in skeletal muscle as well, the assay of CK-MB is not sufficiently specific for cardiac origin. CK-MB used to be the commonly used cardiac marker earlier, till the arrival of Troponin-T assay. This test was widely used by cardiologists in acute coronary syndromes before the advent of Troponin-T. Since Troponin-T assay is now available in most of the hospitals, the use of CK-MB has come down.[15]

CK-MB is not specific to cardiac muscle because there is significant overlap between cardiac and skeletal muscle CK structure. Hence CK-MB assay is not as reliable as Troponin-T for assessing extent of myocardial ischemic injury.

It has been proved in studies that even with a transient myocardial ischemia which causes "reversible" myocardial damage, Troponin-T is released into circulation. This proves the high sensitivity of Troponin-T assay in detecting myocardial injury.[7]

INTRA-OPERATIVE MONITORING OF MYOCARDIAL PROTECTION:

These are the techniques used to monitor both adequacy and uniform distribution of cardioplegia. Myocardial temperature and pH monitoring are the two mainstays of intra-operative monitoring of adequacy of myocardial protection.[1]

Myocardial Temperature monitoring:

Thermocouple needles inserted into the myocardium is the most commonly used technique. Usually a single needle is inserted into the septum and the temperature is monitored. The adequacy of cardioplegia solution is dictated by the temperature attained at

the septum. When rewarming of the septum occurs, it becomes an indication for repeat cardioplegia.

Myocardial pH monitoring:

pH monitoring is not used widely but it is a useful tool to monitor adequacy of myocardial protection. pH monitoring can be done either directly by small pH meters inserted through the myocardium or indirectly through measurement of pH in coronary sinus effluent.

Research level assessment of adequacy of myocardial protection:

For experimental purposes, myocardial biopsy can be taken from animals that are subjected to aortic cross clamping either by transvenous route when the animal is alive or by postmortem studies when the animal is sacrificed. In humans, postmortem biopsies of myocardium may be examined for patchy muscle necrosis, myofibrillar degeneration, etc. for research purposes.

IMPORTANCE OF OUR STUDY:

Since poor myocardial protection and the injury sustained due to ischemia-reperfusion injury has its effects in both immediate postoperative period (unstable postoperative period, prolonged ventilator support, increased inotropic support, prolonged ICU stay, increased mortality rate) as well as in long term results (poor functional class, poor LV function, early mortality), its avoidance will result in overall improvement in patient's postoperative status and also a reduction in mortality. The identification of presence of myocardial ischemic injury and its extent in every individual patient will help to self-evaluate the techniques we follow in myocardial protection. If there is a single test which detects both the presence and the severity of myocardial injury specifically and with 100% sensitivity, that test can be used to evaluate all patients postoperatively both to find

out the cause of poor hemodynamic status as well as for research purposes to evaluate the efficacy of different methods of myocardial protection and different kinds of cardioplegic solutions.

Of all the tests available so far in this category, only Troponin-T evaluation has highest sensitivity and specificity.[9] But the important factor of surgical myocardial injury complicates the practical use of this test. Any surgical incision on the heart causes release of Troponin-T into the circulation and hence Troponin-T elevation is universal after any cardiac surgery. It is important to differentiate Troponin-T elevation due to ischemic damage from that due to surgical incision. Many scientific papers have been published about the significance of Troponin-T values in postoperative period. These papers have proved a fact that the rise of Troponin-T in postoperative period follows a predictable pattern i.e. the initial rise upto a certain level can be considered to correspond to surgical injury and later phases of elevation beyond this level indicates the level of myocardial ischemia-reperfusion injury.

The significance of Troponin-T after cardiac surgery still remains undefined.

This study that we have undertaken is another attempt to find out if the Troponin-T level predicts the severity of ischemic injury differentiating it from surgical injury based on a cut-off value between the two. In other words, our aim was to find out if Troponin-T elevation in post-cardiac surgery patients is predictable or is erratic without any predictability. (by the word “predictable”, we mean “predictable level of troponin-T consistent with the severity of ischemic myocardial injury”)

USEFULNESS OF TROPONIN-T IN CARDIAC SURGICAL PATIENTS:

Troponin-T should be routinely used after open heart surgeries for following reasons:

1. The value of Troponin-T in a postoperative patient tells us about the efficacy of myocardial protection strategies applied in that patient and to review any deficiencies in myocardial protection. In a long term basis, this would help improve the myocardial protection strategies that we follow in our hospital.

2. This test is useful to find out the cause of difficult postoperative period in some patients (unexplained postoperative hemodynamic instability).

3. Identification of high risk patients by high Troponin-T values may direct us to take special care in these individuals so as avoid morbidity or mortality. More duration of intensive care monitoring, special interventions and efficient use of economic resources may be directed to these high risk patients. By these measures, the patient outcome may be improved.

THE NORMAL CUT-OFF VALUES FOR TROPONIN-T:

The cut-off values for Troponin-T for detecting acute cardiac ischemic events (non-surgical) are well known but these values are not applicable for cardiac postoperative status because Troponin-T levels are invariably elevated in all patients undergoing cardiac surgery, irrespective of the complexity of surgery. Hence we need to find out the cut-off value for Troponin-T in post cardiac surgery status (specifically for each type of cardiac surgery). Below this cut-off level, the values would indicate incisional elevation and beyond this, would indicate ischemic necrosis.

The standard textbook in cardiology, Hurst's The Heart, denotes the normal and abnormal values for Troponin-T as below:

upto 0.01ng/ml (normal)

Upto 0.09 (borderline)

>0.1 (Indicative of myocardial infarction).

But, these values are not applicable to patients who have undergone cardiac surgery as the postoperative values of Troponin-T are usually much exceeded than 0.1ng/ml. Hence, new cut-off values should be derived for cardiac surgical patients, (more specifically, cut-off values for each type of cardiac surgery). Many previous studies have found that when the levels go beyond 13ng/dl, the mortality rate goes steeply high.

TROPONIN-T ASSAY METHOD:

Troponin-T in blood is assessed by immunometric one-step sandwich technique. The testing is based on polyclonal antibodies specifically developed against epitopes on cTnT molecule. These epitopes differ significantly between cardiac Troponins (cTnT) and skeletal Troponins.

In this method, polyclonal antibody to epitopes of cardiac Troponin-T is immobilized in polyvinylchloride test tubes. Troponin-T standards (control) or serum samples and peroxidase-labeled anti-Troponin-T monoclonal antibody is added to these test tubes. When incubated, Troponin-T molecules are adsorbed onto polyclonal antibody (which are in solid-phase) and to monoclonal antibody-enzyme complex (which are in liquid phase). The unbound peroxidase-labeled monoclonal antibodies are removed by washing. Now, the antibody-enzyme complexes which are adhered to the tubes correspond to Troponin-T level in that patient. The amount of enzyme immobilized is the direct measure of bound Troponin-T and this is measured by spectrophotometer (by peroxidase substrate conversion at 405 nm wavelength).[13]

DETAILS OF THE STUDY

The study was intended to find out if Troponin-T assay in postoperative status was useful as an indicator of myocardial ischemic injury sustained during aortic cross clamp and cardioplegic arrest.

To analyse the correlation between myocardial ischemic injury and Troponin-T level, we decided to correlate the following variables with the level of Troponin-T.

1. Aortic cross clamp time
2. CPB time
3. CP interval time
4. Longest Time Off Cardioplegia (LTOC)
5. Average Time between each cardioplegia (ATOC)
6. Postoperative duration of ventilation
7. Duration of ICU stay
8. Inotropic support required
9. Post op ECG evidence of myocardial ischemia
10. ECHO evidence of myocardial ischemia
11. Clinical evidence of failure (evidence of pulmonary edema, requirement of excess diuretics, etc)
12. Postoperative functional status(NYHA)
13. Mortality

The mortality rate following open heart surgeries are too low to be used as a marker of poor surgical results in a small scale study. Hence, we depend on other evidences of myocardial injury to establish correlation between poor myocardial protection and poor postoperative outcomes.

EXCLUSION CRITERIA:

Those patients with severely depressed cardiac function (EF<40%) require special care during myocardial protection measures. And also there is a rise in Troponin-T level in blood of patients in failure. Hence these patients were excluded from the study.

As already mentioned, those patients who have evidence of coronary artery disease (ECG or Echo evidence) were excluded from the study since perioperative MI may cause a rise in Troponin-T elevation. Patients older than 40 years are routinely evaluated with coronary angiogram and those who have significant coronary artery disease are also excluded from the study.

Patients who had already undergone Closed Mitral Commissurotomy (CMC) and now undergoing mitral valve replacement surgery were excluded, as during dissection of adhesions, direct surgical injury to myocardial tissue occurs.

Patients with more than mild AR were also excluded.

Since Troponin-T elevation occurs in patients with chronic renal failure due to unknown reasons (explained below), CKD patients were excluded from the study.

Patients with elevated liver function tests were also excluded since the excretion of Troponin-T may be affected in these patients.[7]

THE TIMING OF THE TROPONIN-T ESTIMATION IN THIS STUDY:

Since Troponin-T levels usually reach their peak values at around 18-24 hours after an ischemic event, and then start to decline, a single estimation of its value at 24 hours is used in this study. Most of the previous studies to evaluate the correlation of Troponin-T with myocardial ischemic time have used this same kind of testing (i.e. a single measurement at 24 hours after surgery, though some of the studies have done Troponin-T assay at 20 hours)

It has been proved in studies that even with a transient myocardial ischemia which causes "reversible" myocardial damage, Troponin-T is released into circulation. This proves the high sensitivity of Troponin-T assay in detecting myocardial injury.[7]

THE STANDARD STEPS OF A MITRAL VALVE REPLACEMENT SURGERY IN OUR HOSPITAL:

Under General Anesthesia, median sternotomy is done. Thymus is mobilized. Pericardial cradle is created. Cardiopulmonary bypass is established with bicaval and aortic cannulae after heparinisation. Alpha-stat acid-base management protocol is followed. Heparin is administered at a dose of 300 U/kg body weight. Activated Clotting Time (ACT) is tested after 5 minutes and it is maintained above 480 sec throughout cardiopulmonary bypass. Priming solution (for an adult) is prepared by adding 500ml of Ringer-Lactate solution + 500ml of Hetastarch . 100ml of Inj.Mannitol (20%), 50 ml of Inj.Sodium Bicarbonate and 2ml of Inj.Dexamethasone are added to this solution. Heart is cooled to 32 degree Celsius gradually over 5 minutes. Aorta is cross clamped at 32 degree C. Antegrade cardioplegia is administered through a 12 Fr cannula in the ascending aorta with digitally guided aortic root pressure, for a duration of 2-3 minutes. Cardioplegic solution is prepared with Inj.Plegiocard. 4:1 blood cardioplegia is prepared. This solution is administered at 4 degree Celsius. The left atrium is opened to avoid distension of the left heart. After cardioplegia administration and electromechanical quiescence of the heart is obtained, ice slush is poured into pericardial cavity and its spread underneath the heart is ensured. Cardioplegia is repeated every 20-30 minutes or upon seeing the cardiac activity, depending on whichever is earlier. Ice slush is applied after every cardioplegia administration. When the surgery is predicted to be over within 10 minutes ice slush is avoided during the last cardioplegia. Core cooling is done upto 28 degree Celsius. Once left atrium is opened, any clot in the cavity or in LA appendage is removed. LA appendage exclusion is done, in

patients with LA/LA appendage clot, with circumferential sutures taken on endocardial side of LAA using 3-0 prolene. Anterior mitral leaflet (AML) and posterior mitral leaflet and subvalvular apparatus are examined. PML is fully or partially preserved if anatomy is favorable. AML and its chordate are removed. Intermittent horizontal mattress sutures are taken from atrial side (so that the pledgets lie on atrial side and the valve lies intra-annularly) using 2-0 Ethibond pledgetted sutures with 13 mm round-bodied half circle needles. The valve sizer is used to measure the annulus size and valve is selected according to it. Selection of tilting disc or bileaflet valve depends on surgeon's preference as well as the availability of valve at that time (valves being supplied by the TNMSC). All the suture needles are subsequently passed through the sewing ring of the prosthetic valve and the valve is parachuted to the annular position. The sutures are tied securely with 5 knots. After mitral valve implantation, the mobility of the prosthetic valve leaflet(s) is tested. Any subvalvular chordae or other structure interfering with the movement of the leaflet is cut away or else the valve is rotated within the sewing ring such that the mobility is unrestricted. Usually, a tilting disc valve is positioned with its larger orifice facing posteriorly if PML was excised and anteriorly if PML is preserved. A bileaflet valve is positioned in anti-anatomical position. Left atrium is closed in two layers using 3-0 prolene and before tying the last knot, the LA is de-aired. The CP cannula in ascending aorta is used for de-airing and blood is allowed to be ejected through this for 5 minutes and later it is connected to pump with 300ml/min reverse flow. Aortic cross clamp is removed with head end down and with carotid compression and with the pump flow reduced to 0.5 lit/min. This flow rate is gradually increased to normal flow over 2-3 minutes. Defibrillators are used when necessary. The heart is supported with pump for a duration of 1/3rd of total cross clamp time. Heart is weaned from cardiopulmonary bypass gradually. CP cannula, SVC and IVC cannulae are removed and Protamine infusion is started. When half of the protamine infusion is completed, aortic cannula is removed. Protamine dose is calculated according to

the total dose of heparin given during the surgery (1.2mg for 1mg of heparin) also considering the ACT value and the time interval between heparin administration and protaminisation. Intercostal and/or mediastinal drainage tubes are placed. After hemostasis, sternum is approximated with 6 metric steel wires (in an adult); subcutaneous layer approximated with 2-0 Vicryl and skin with subcuticular absorbable sutures. The inotropic support is started only when it is indicated according to the hemodynamic status and not on a regular basis. Postoperatively, patient is shifted to Intensive Care Unit where each patient is cared by a single nurse.

CARDIOPLEGIC METHOD FOLLOWED IN OUR INSTITUTION:

Antegrade, intermittent, cold and blood cardioplegia is the routine cardioplegia method followed in our institution for all cases of Mitral Valve Replacement (MVR) surgeries. 4:1 blood cardiolplegia is administered at a dose of 20ml/kg for first time and then 10ml/kg subsequently.

ANESTHESIA:

Patients are given premedication and pre-operative antibiotics 30 minutes before surgery. Induction is done Inj.Thiopentone and Inj. Fentanyl is used as a narcotic. Inj.Vecuronium is used for paralysis. Inhalant anesthetic, Isoflurane is used at 1MAC. It has been proved in studies that Isoflurane has pre-conditioning effect on the heart and its use is associated with lower postoperative Troponin-T levels.

POST-OPERATIVE CARE:

Patients are monitored in cardiothoracic ICU where each patient is monitored by a single nurse. The team leader of the ICU is a cardiothoracic surgeon. Inotropic supports are not a routine protocol in our hospital but are started only on the basis of hemodynamic status. Patients are extubated when they are hemodynamically stable, fully alert and there is

no significant post-operative bleeding. Some of the surgical units have a protocol to extubate them only on the 1st post-operative day in the morning hours. Intravenous unfractionated Heparin (5000 units) is administered 10 hours after surgery if there is no significant drain and Acinocoumerol is started in the evening of 1st postoperative day. Patients are monitored in this ICU for minimum 2 days after surgery. When patient is stable, patient is shifted to step-down ICU where each nurse monitors 5 patients.

TROPONIN-T LEVEL ESTIMATION

Troponin-T analysis was done when 24 hours had passed after surgery. For this purpose, 2ml of blood is collected from the patient and is sent to the lab in a test tube (The cost of the test was borne by the prinicipal investigator). The testing was done in a private lab (Hi-Tech Labs) and all the 51 samples were analysed in the same laboratory. The blood sample was centrifuged immediately and the serum was used for estimation of Troponin-T level by Electro-chemiluminescence (ECLIA) method. The results are given in ng/ml units.

MATERIALS AND METHODS

This prospective study was undertaken as an analytical study to find out the significance of post-operative Troponin-T level as a marker of myocardial ischemic injury in mitral replacement surgeries, in cardiothoracic surgery department of Rajiv Gandhi Government General Hospital, Chennai-600003, from April 2012 to March 2013. Hospital Ethical Committee approved this study to be conducted in Rajiv Gandhi Govt General Hospital. Patients were well informed about the nature of the study and consent was obtained in written format for withdrawal of 2 ml of blood and Troponin-T estimation.

INCLUSION CRITERIA

Patients who were to undergo Mitral Valve Replacement Surgeries during the above said period were included in the study. Both Rheumatic and Non-rheumatic pathologies were accepted for the study. Both stenotic (MS) and regurgitant (MR) lesions (or a combined of two) were included. Only patients aged more than 13 years were included in the study.

EXCLUSION CRITERIA

1. Patients who have evidence of coronary artery disease
2. Re-do mitral valve surgeries (Post-CMC)
3. Poor left ventricular function (EF<40%)
4. LV diastolic dimension >7.0 cm
5. Renal failure
6. Hepatic failure
7. Patients with more than mild AR (aortic regurgitation)

METHODOLOGY

The preoperative, per-operative and post-operative details were personally collected by the investigator by direct communication with the patient and by assisting during the surgery and also following-up the patient in post-operative period. The data regarding significant events after discharge of the patients were also traced by phone communication and by follow-up in the out-patient department.

The information and data collected for each patient were entered in the proforma specially designed for this study.

The following information/data were collected from each patient.

1. Name, age, sex, IP number, Date of admission
2. ECG and Echo findings- Echocardiogram is done both by cardiologists and cardiothoracic surgeons.
3. Pre-operative functional class (NYHA classification was used)
4. Presence or absence of Atrial fibrillation
5. Total cross clamp time
6. Number of times cardioplegia was administered
7. Longest time off cardioplegia (Longest time between any two consequent cardioplegia)
8. Average time interval of cardioplegia (time interval between consequent cardioplegia doses)
9. Cardiopulmonary bypass (CPB) time
10. Requirement of DC shocks: it has been proved in studies that, though external defibrillator application causes elevation of Troponin-T, internal cardioversion does not cause any such elevation.

11. Requirement of post-operative inotropic support. This was classified into three categories for the purpose of ease of calculation and better understanding.

Drug	Minimal	Intermediate	High
Dopamine	<5ug/kg/min	6-10ug/kg/min	>11ug/kg/min
Adrenaline	<0.05ug/kg/min	0.06-0.1ug/kg/min	>0.11ug/kg/min
Isoprenaline	<0.05ug/kg/min	0.06-0.1ug/kg/min	>0.11ug/kg/min

12. Duration of inotropic supports (in days)
13. Duration of postoperative ventilation (in hours)
14. Duration of ICU stay (in days)
15. Duration of hospital stay after surgery (in days)
16. ECG or echo evidence of myocardial ischemia. A new q wave of more than 0.1 mV, or ST-T changes in two consequent leads suggestive of ischemia were taken as positive evidences of perioperative MI or significant ischemic injury. ECG interpretation was done by cardiologists in association with cardiothoracic surgeons. Postoperative echo was performed by cardiologists in the immediate post-op period if patient is hemodynamically unstable but only after 7 days if patient is stable.
17. Clinical evidence of failure: patient was examined by the investigator for presence of any signs of cardiac failure like, pulmonary crepitations, pedal edema, tachycardia, dyspnoea, mental obtundation, cold peripheries, high CVP, reduced urine output, etc., Patient's symptoms were also taken into account.
18. Ejection fraction of left ventricle: this was categorized into three varieties.

    EF 41-50% - mild dysfunction

    EF 31-40% - moderate dysfunction

EF <30% - severe dysfunction

19. Postoperative NYHA status: patients were classified into 3 categories: those who got improved after surgery and those who didn't get any improvement and those who got worsened after surgery.
20. Requirement of IABP
21. Mortality: the cause of mortality was assessed and was ascertained whether it is due to cardiac cause or non-cardiac cause.

ANALYSIS METHODS

Data were analysed with the help of a doctor specialized in statistics.

Descriptive statistics: mean± standard deviation was calculated.

Correlation for continuous variables was done. Chi-square/Fischer's test was done for categorical variables. Independent 't' test was done to look for significant different between 2 groups. ROC (Receptor Operator Characteristic) curve was used to determine the cut-off level of troponin-T at which levels, the postoperative complications occur more. By ROC curve, the level was fixed at 0.6 ng/ml.

Data was entered in Microsoft Excel Spreadsheet and was analysed using SPSS (Statistical Package for Social Science) version 16.

RESULTS

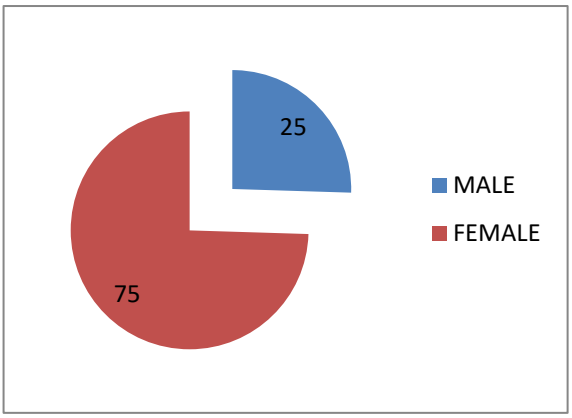
AGE DISTRIBUTION:

The Age group extended from 15 years to 61 years.

Mean age was **32.92 ± 12.02** years and median age was **32 years**.

SEX DISTRIBUTION:

Among the study participants, 75 % were females



LESION-WISE CLASSIFICATION:

16 (31.4%) patients had mitral stenosis

13 (25.5%) patients had mitral regurgitation

22 (43.1%) patients had both mitral stenosis and regurgitation

17 (33.3%) patients had pre-operative atrial fibrillation

2 (3.9%) patients had LA clot.

NUMBER OF CP (NUMBER OF TIMES CARDIOPLEGIA WAS ADMINISTERED):

1 – 1 (2%)

2 – 30 (58.8%)

3 – 18 (35.3%)

4 – 2 (3.9%)

Average: 2.4

Median: 2

For those patients, who received 1 or 2 cardioplegias, the average Troponin-T level was 0.676 ng/ml.

For those, who received 3 or 4 cardioplegias, the average troponin-T value was 0.706 ng/ml.

TOTAL CROSS CLAMP TIME:

Average: **68 ± 2 minutes**

Median: 70 minutes

Longest: 87 minutes

Shortest: 28minutes

Aortic cross clamp time	Number of patients	%	Average Troponin-T value for this group
≤70 minutes	27	52.9%	**0.567 ng/ml**
> 70 minutes	24	47.1%	**0.821 ng/ml**
Total	51	100%	

The above table shows that Troponin-T levels are elevated with increasing duration of aortic cross clamp time.

LONGEST TIME OFF CARDIOPLEGIA (LONGEST INTERVAL BETWEEN CARDIOPLEGIAS IN A SINGLE PATIENT):

Mean: 28 ± 1 minutes

Median: 28 minutes

Longest: 38 minutes

Shortest: 22 minutes

Longest Time Off Cardioplegia	Number of patients	%	Average Troponin-T value for this group
≤ 28 minutes	29	56.8%	**0.661 ng/ml**
>28 minutes	22	43.1%	**0.723 ng/ml**
Total	51	100	

The above shows that when the interval between two cardioplegias is prolonged, Troponin-T levels are simultaneously elevated.

AVERAGE TIME INTERVAL OF CARDIOPLEGIA:

Mean: 26 ± 1 minutes

Median: 26 minutes

Maximum : 34 minutes

Minimum : 21 minutes

Average interval between cardioplegias	Number of patients	%	Average Troponin-T value for this group
≤ 26 minutes	27	53%	**0.594 ng/ml**
> 26minutes	24	47%	**0.739 ng/ml**
Total	51	100%	

The above table shows that when the interval between two cardioplegias is prolonged, there is increased troponin-T release.

Lichtenstein et al, has used these two parameters in his study, to assess the efficacy of intermittent warm blood cardioplegia.

LTOC- Longest Time Off Cardioplegia (Longest single ischemic time in a patient)

PTCO- Percentage Time Off Cardioplegia[25]

CPB DURATION:

Average CPB duration: **97 ± 2 minutes**

Maximum : 140 minutes

Minimum : 57 minutes

CPB duration	Number of patients	%	Average Troponin-T value for this group
≤97 minutes	21	41.1%	**0.658 ng/ml**
>97 minutes	30	58.8%	**0.709 ng/ml**
total	51	100	

The above table shows that when CPB duration is increased, Troponin-T levels are elevated.

REQUIREMENT OF INOTROPIC SUPPORTS:

Inotropic support	Number of patients	%	Average Troponin-T value for this group
Nil	15	29.4	**0.522 ng/ml**
Minimal / Intermediate	30	58.8	**0.729 ng/ml**
High	6	11.8	**0.894 ng/ml**
Total	51	100	

From the above table, it is evident that higher doses of inotropes are required in those patients whose Troponin- T values are high.

DURATION OF INOTROPIC AGENTS:

37 (72.5 %) patients required inotropic for ≤ 2 days. Their average Troponin-T value was: **0.59 ng/ml**.

14 (27.5) patients required inotropic support for more than 2 days. Their average Troponin-T value was: **0.93 ng/ml.**

Duration of inotropic support	Number of patients	%	Average Troponin-T value for this group
≤ 2days	37	72.5%	**0.59 ng/ml**
> 2 days	14	27.5%	**0.93 ng/ml**
Total	51	100	

DURATION OF VENTILATION:

44 (86.3%) patients required ventilation for less than 24 hours and their average Troponin-T value was: **0.61 ng/ml.**

7 (13.7%) patients required ventilation for more than 24 hours and their average Troponin-T value was: **1.17 ng/ml.**

Duration of ventilator support	Number of patients	%	Average Troponin-T value for this group
Less than 24 hours	44	86.3%	**0.61 ng/ml**
More than 24 hours	7	13.7%	**1.17 ng/ml**
Total			

RELATIONSHIP BETWEEN DC SHOCK AND TROPONIN-T VALUES:

9 patients received DC shock after cross clamp release for defibrillation. For those patients who received DC shocks, the average Troponin-T value was: **0.85 ng/ml**. [Minimum: 0.32 and Maximum: 1.90]

42 patients did not receive DC shock. For those who did not require DC shocks, the average Troponin-T value was: **0.65 ng/ml** [Minimum: 0.12 and Maximum: 1.88]

This data suggests that DC shock may be a cause for Troponin-T elevation.

REQUIREMENT OF IABP:

Only one patient required IABP support in the postoperative period and her Troponin-T value was 0.517 ng/ml.

POST-OPERATIVE EVIDENCE OF FAILURE:

Postop cardiac failure	Number	%	Average troponin-T value for this group
No	40	78.4	**0.607 ng/ml**
Yes	11	21.6	**0.981 ng/ml**
Total	51	100	

40 patients had no evidence of cardiac ischemia/failure (ECG/ECHO/clinical) postoperatively and their average Troponin-T value was **0.607 ng/ml.**

11 patients had evidence of cardiac failure (ECG/ECHO/clinical) postoperatively and their average Troponin-T value was **0.981 ng/ml.**

ICU STAY:

28 (54.9 %) patients had ICU stay of ≤ 5 days. Their average Troponin-T value was **0.655** ng/ml.

23 (45.1 %) patients had ICU stay of > 5 days. Their average Troponin-T value was **0.727** ng/ml.

Mean ICU stay – 5.29 days

Median ICU stay – 5 days

(The average duration of ICU stay is notably high because it is our hospital policy to retain the patients in ICU for an average of 5 days)

ICU stay	Number of patients	%	Average Troponin-T level for this group
≤ 5 days	28	54.9%	**0.655 ng/ml**
> 5 days	23	45.1%	**0.727 ng/ml**
Total	51	100	

TOTAL HOSPITAL STAY AFTER SURGERY:

24 (48.8 %) patients (excluding 2 deaths) had ≤ 12 days of hospital stay.

25 (51.2 %) patients had > 12 days of hospital stay.

For patients who had less than 12 days of hospital stay, the average Troponin-T value was: **0.51ng/ml .**

For patients, who had more than 12 days of hospital stay, average Troponin-T value was: **0.82 ng/ml.**

Total hospital stay after surgery	**Number of patients**	**%**	**Average Troponin-T level for this group**
≤ 12 days	24	48.8%	**0.510 ng/ml**
> 12 days	25	52.2%	**0.820 ng/ml**
Total	49		

NYHA STATUS:

Pre-op NYHA	Frequency	Percent
II	5	9.8
III	38	74.5
IV	8	15.7
Total	51	100.0

Post-op NYHA	Frequency	Percent
I	17	33.3
II	25	49.0
III	7	13.7
IV	2	3.9
Total	51	100.0

Postoperatively, 42 patients were in NYHA I/II. Their mean Troponin T value was **0.57** ng/ml

7 patients were in NYHA III/IV. Their mean Troponin T value was **1.26** ng/ml.

NYHA (Post- OP)	**Frequency**	**Percent**	**Average Troponin-T for this group**
I&II	42	82.3%	**0.57 ng/ml**
III&IV	9	17.6%	**1.26 ng/ml**
	51	100%	

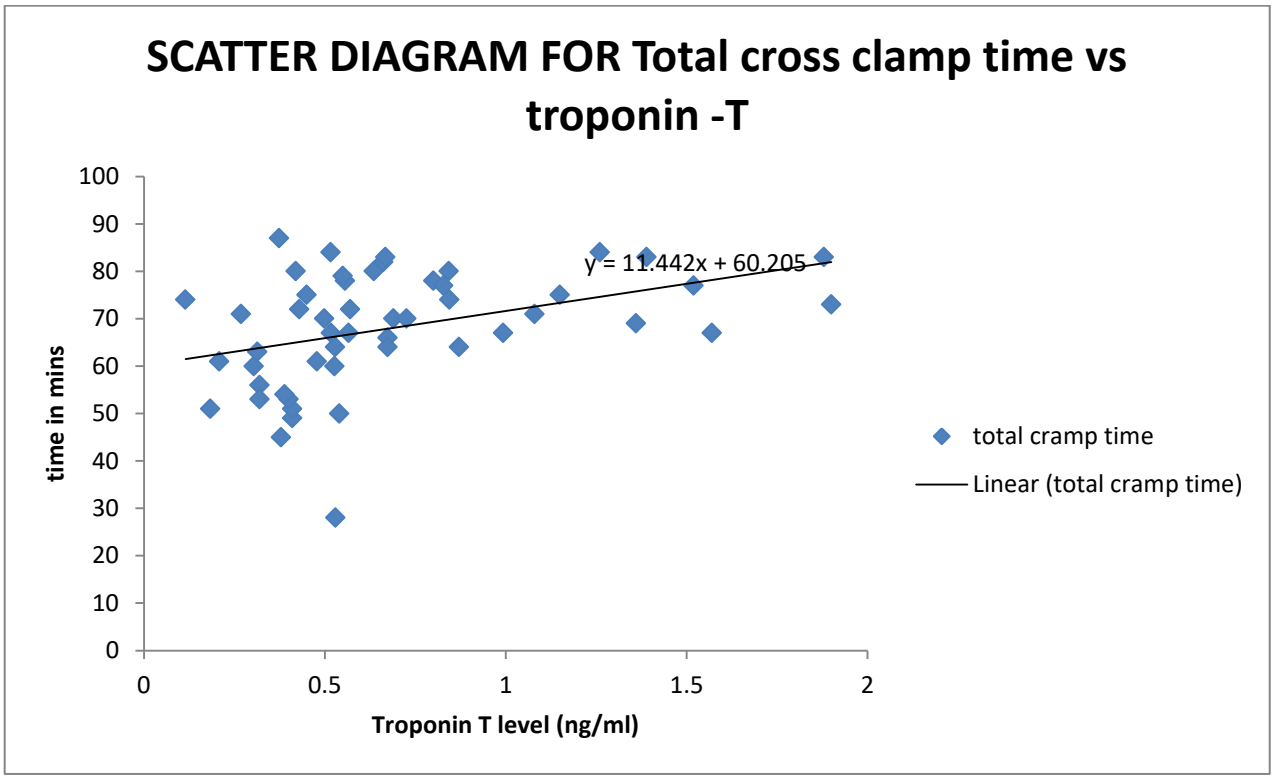
This table shows that when Troponin-T level is high, the patient is more likely to be in NYHA Class III or VI.

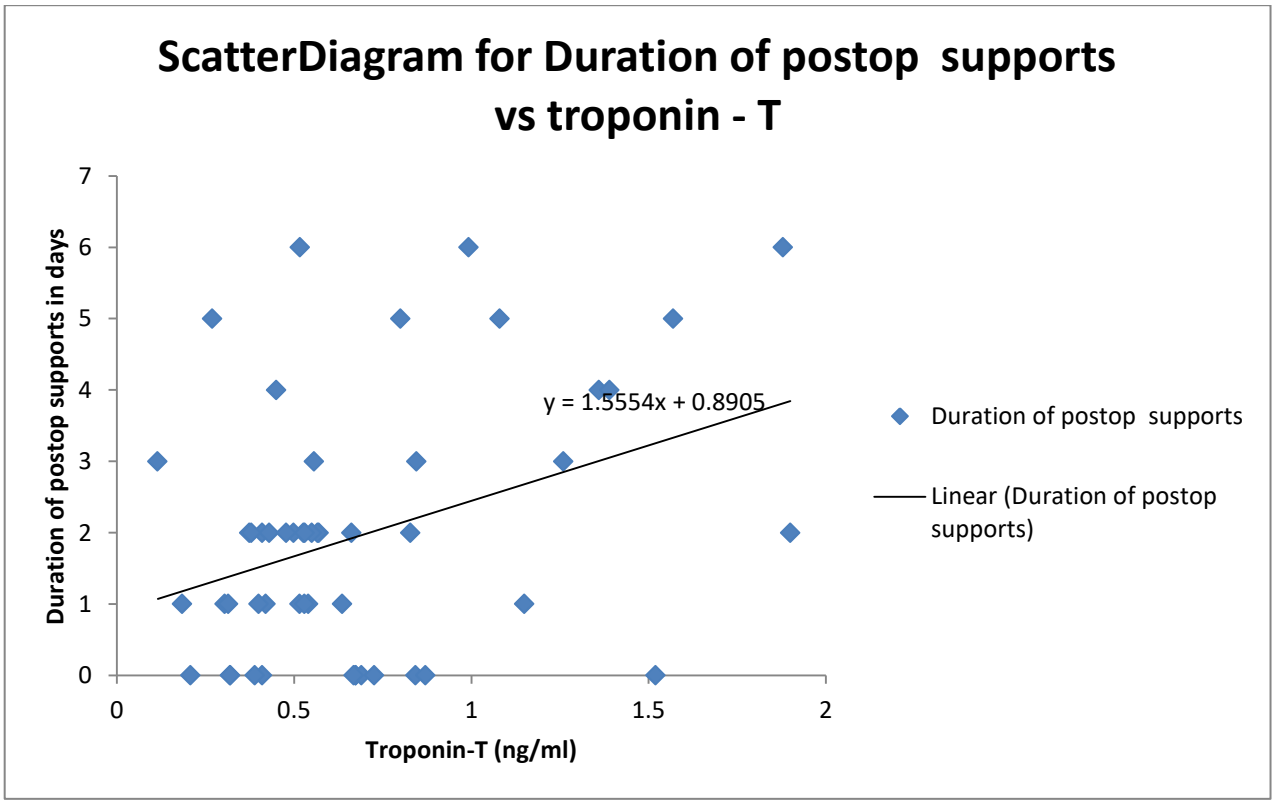
MORTALITY:

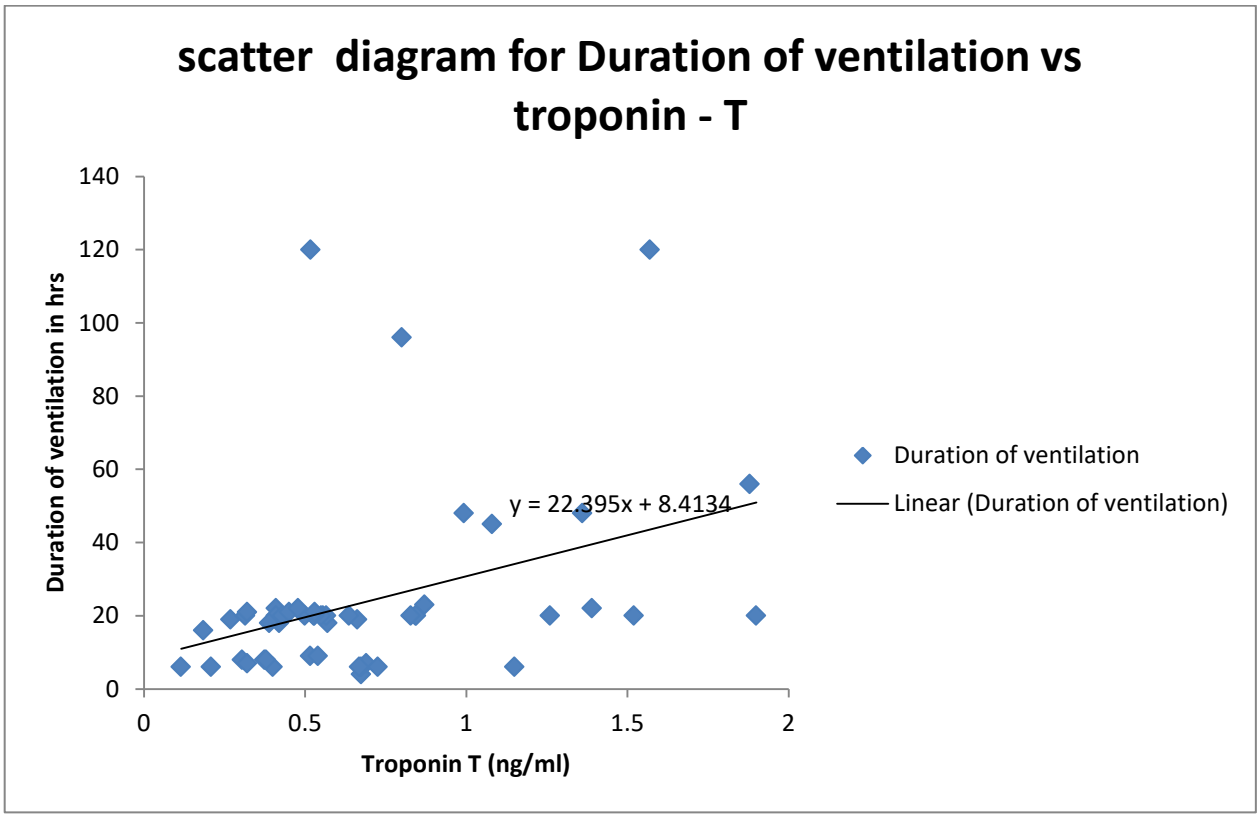
Only two patients died in our study population. Their Troponin-T values were 1.570 and 0.80 ng/ml.

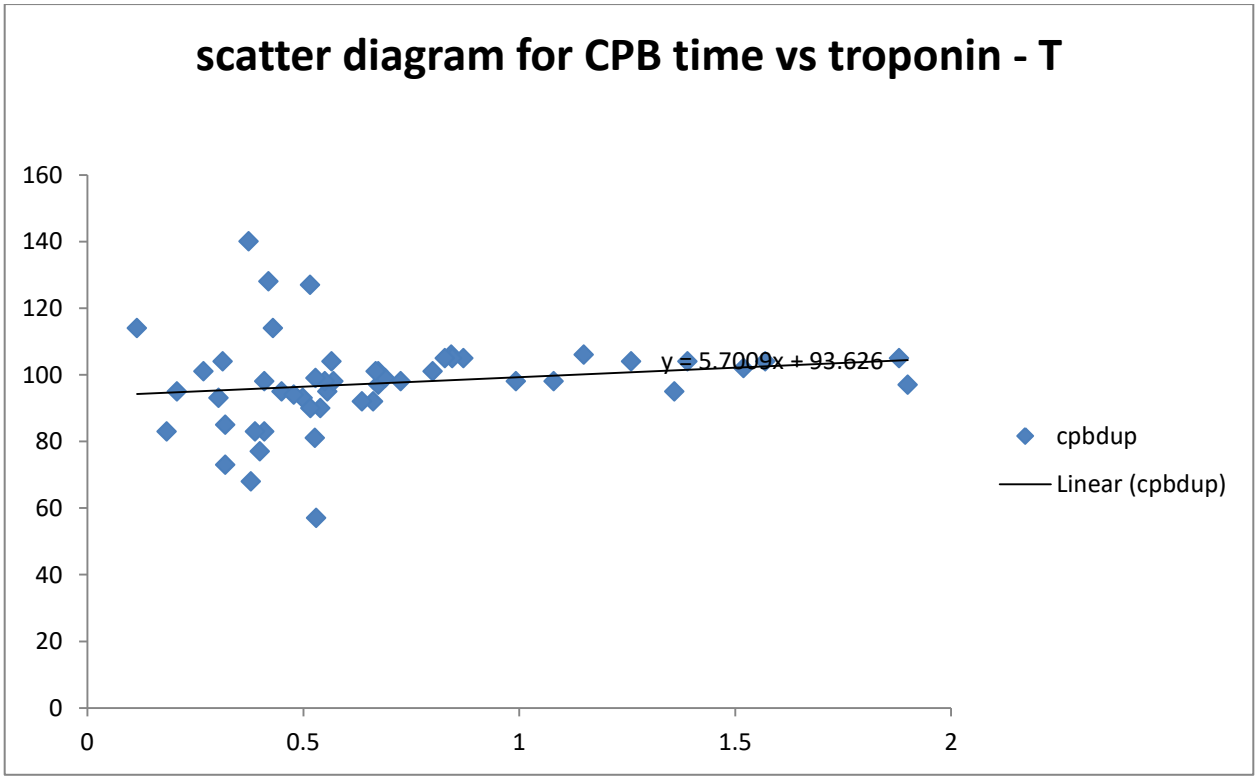
DESCRIPTIVE STATISTICS FOR THE VARIABLES:

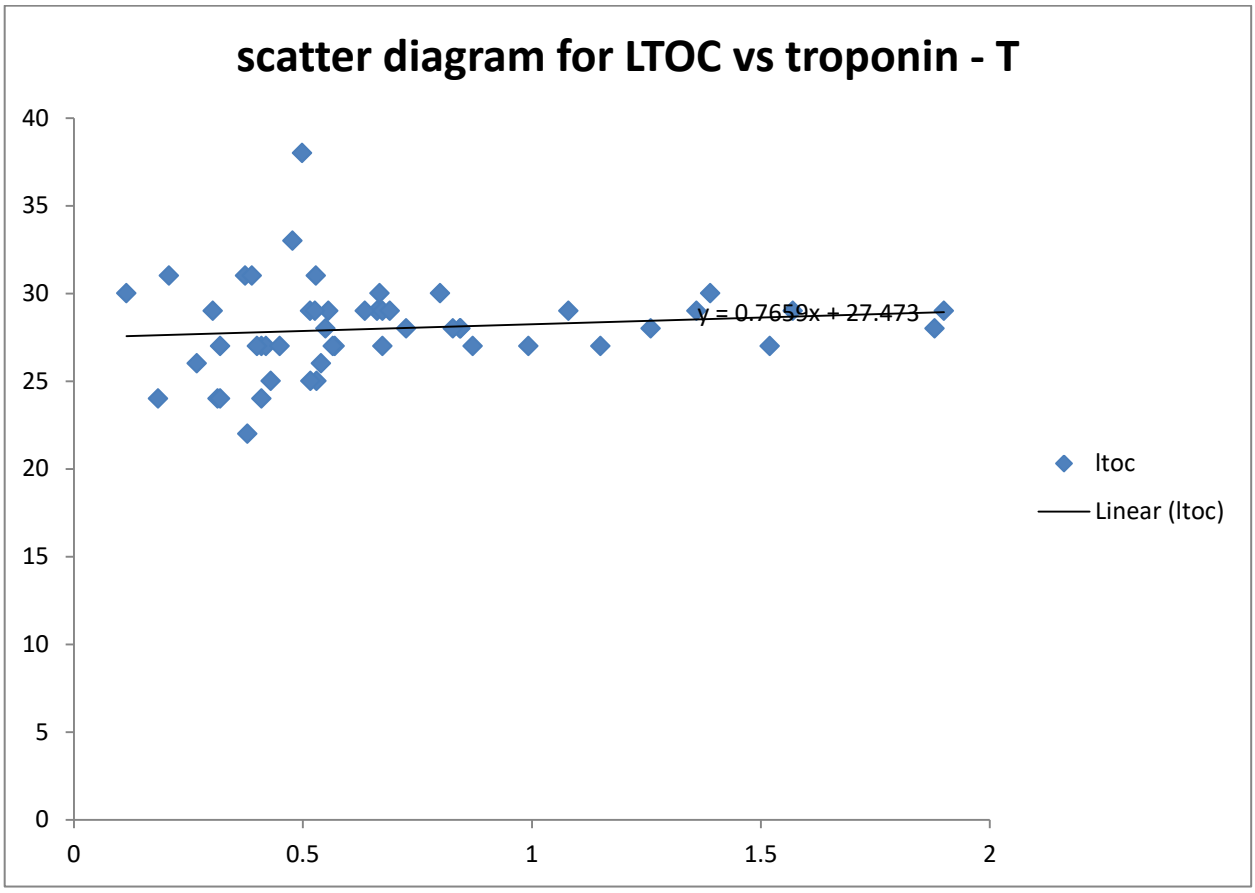
	N	Minimum	Maximum	Mean	Std. Deviation
Age	51	15	61	32.92	12.020
Sex	51	1	2	1.75	.440
Troponin T	51	.12	1.90	.6881	.41895
Cross_cramp_time	51	28.00	87.00	68.0784	12.17020
Cpb duration	51	57.00	140.00	97.5490	13.89146
LTOC	51	22.00	38.00	28.0000	2.59230
ATOC	51	21.00	34.00	25.9804	2.59608
No_of_CPs	51	1.00	4.00	2.4118	.60585
Duration_of_postop__supports	51	.00	6.00	1.9608	1.79956
Duration_of_ventilation	51	4.00	120.00	23.8235	24.98536
Postop_EF	51	40.00	84.00	62.9216	14.17581
ICU_stay	51	3.00	12.00	5.2941	2.44372
Total_hospital_stay_after_surgery	51	7.00	30.00	12.7843	4.80963

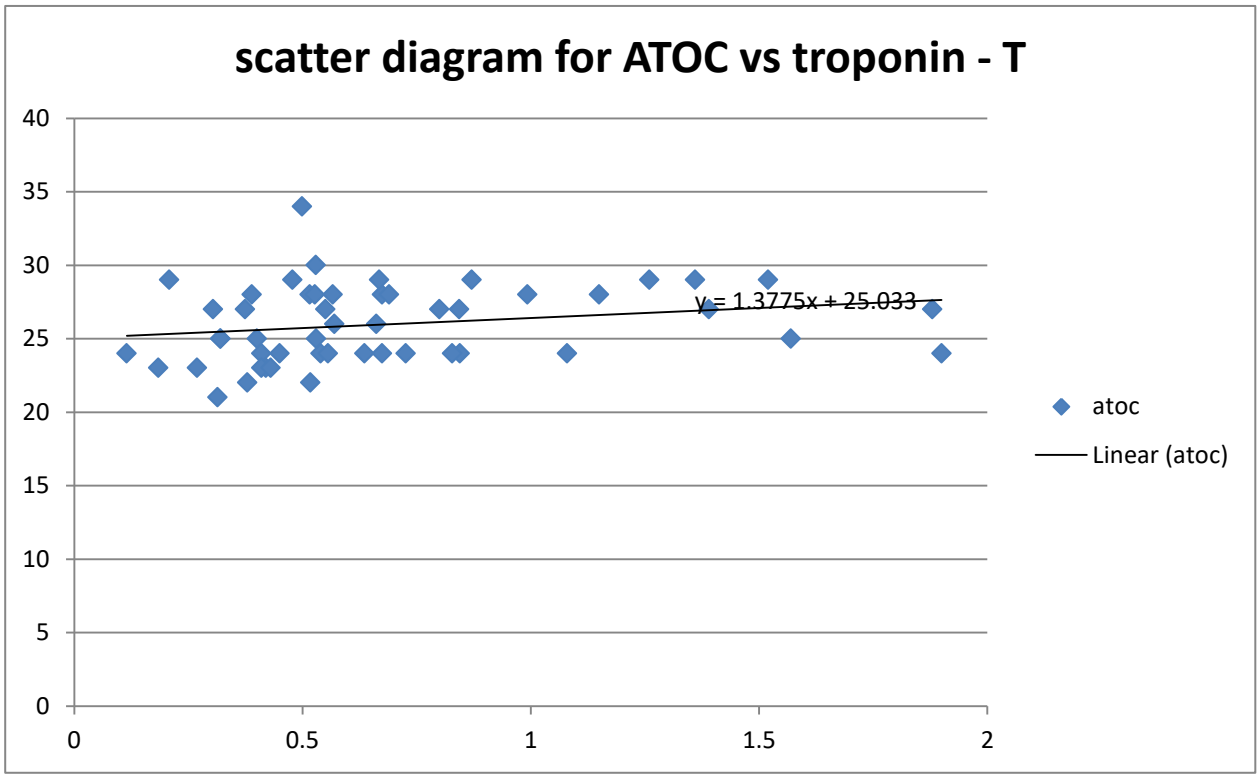

SCATTER DIAGRAM FOR Total cross clamp time vs troponin -T
time in mins
Troponin T level (ng/ml)
y = 11.442x + 60.205
total cramp time
Linear (total cramp time)

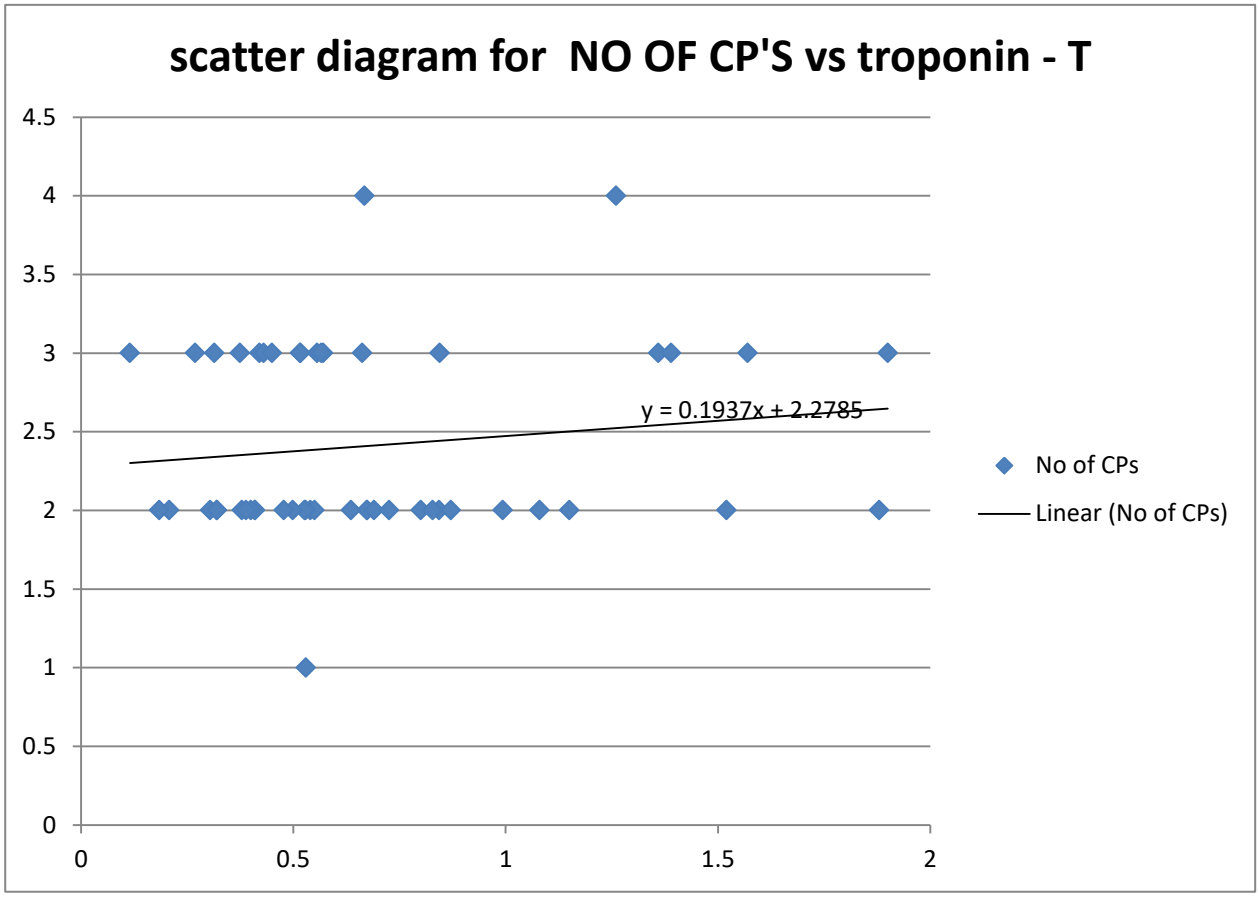

ScatterDiagram for Duration of postop supports vs troponin - T
Duration of postop supports in days
Troponin-T (ng/ml)
y = 1.5554x + 0.8905
Duration of postop supports
Linear (Duration of postop supports)


scatter diagram for Duration of ventilation vs troponin - T
Duration of ventilation in hrs
140
120
100
80
60
40
20
0
0
0.5
1
1.5
2
Troponin T (ng/ml)
y = 22.395x + 8.4134
Duration of ventilation
Linear (Duration of ventilation)


scatter diagram for CPB time vs troponin - T
160
140
120
100
80
60
40
20
0
0
0.5
1
1.5
2
y = 5.7009x + 93.626
cpbdup
Linear (cpbdup)


scatter diagram for LTOC vs troponin - T
y = 0.7659x + 27.473
ltoc
Linear (ltoc)
0
5
10
15
20
25
30
35
40
0
0.5
1
1.5
2


scatter diagram for ATOC vs troponin - T
y = 1.3775x + 25.033
atoc
Linear (atoc)
0
5
10
15
20
25
30
35
40
0
0.5
1
1.5
2


scatter diagram for NO OF CP'S vs troponin - T
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
0.5
1
1.5
2
y = 0.1937x + 2.2785
No of CPs
Linear (No of CPs)

DESCRIPTIVE STATISTICS FOR THE VARIABLES

Troponin-T level correlation	Pearson correlation	Significance (2-tailed)	Total number
Total cross clamp time	**0.394**	**0.004**	51
CPB duration	0.172	0.228	51
LTOC	0.124	0.387	51
ATOC	0.222	0.117	51
Number of CP	0.134	0.349	51
Postop supports	0.263	0.062	51
Duration of postop supports	**0.362**	**0.009**	51
Duration of ventilation	**0.376**	**0.007**	51
Requirement of IABP	-0.06	0.684	51
ECG/ECHO evidence of ischemia	**0.429**	**0.002**	51
Clinical evidence of cardiac failure	**0.400**	**0.004**	51
Post op Ejection Fraction	**0.605**	**0.001**	51
ICU stay	0.033	0.818	51
Total hospital stay after surgery	0.142	0.319	51
mortality	0.242	0.087	51

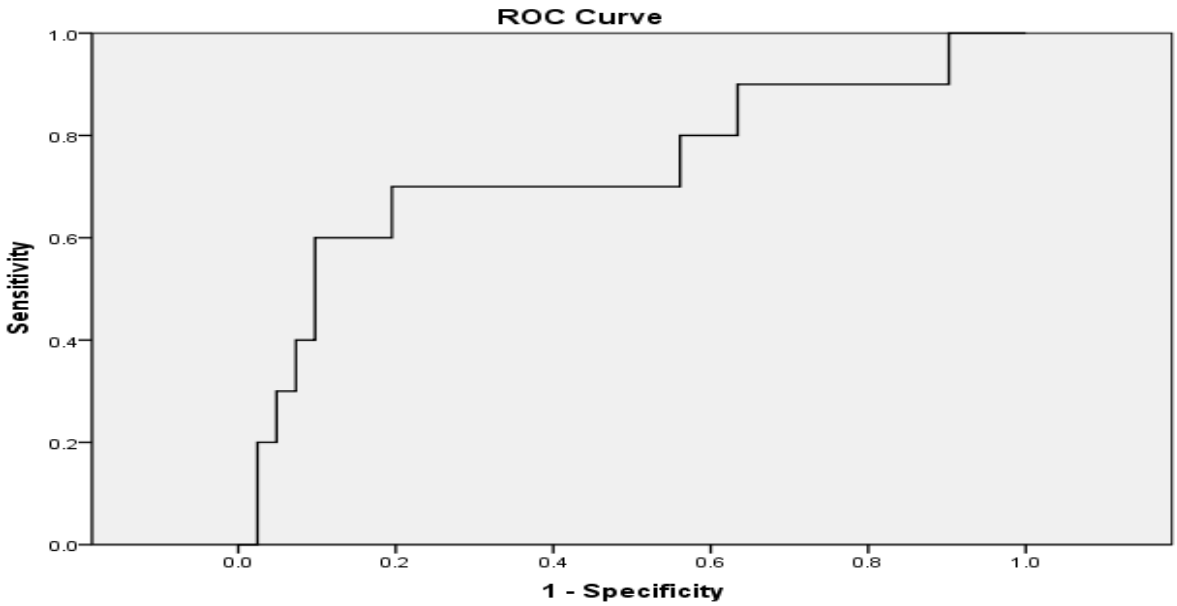
Significant at <0.05

From the above table, it can be seen that the Troponin-T level has significant correlation with the following variables:

1. Total cross clamp time (p value 0.004)
2. Duration of postoperative supports (p value 0.009)
3. Duration of ventilation (p value 0.007)
4. ECG/ECHO evidence of ischemia (p value 0.002)
5. Clinical evidence of cardiac failure (p value 0.004)
6. Postoperative Ejection Fraction (p value 0.001)

ROC (RECEIVER – OPERATOR - CHARACTERISTIC) CURVE

Post op_failure	Number
YES	11
NO	40

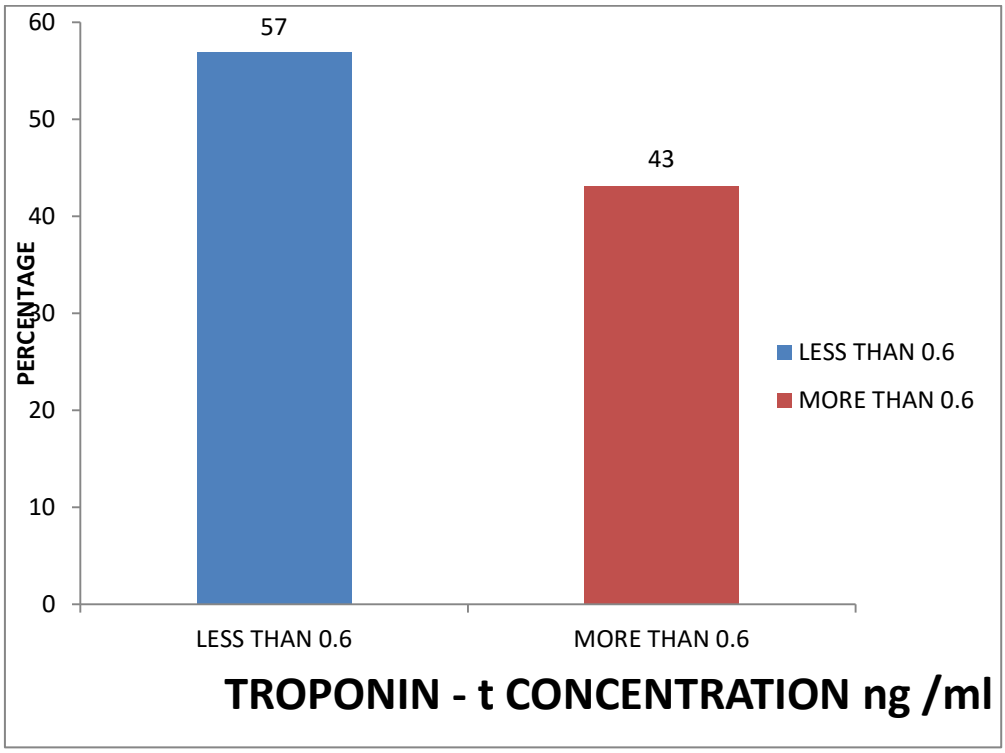


Test Result Variable(s): TroponinT

Area
.734

Based on the above ROC curve for post operative complications and troponin T levels, the optimum cut off level for troponin T is **0.6 ng/ml** (Area under the curve is 73.4%)

INDEPENDENT T-Test (Test of significance between two groups)



GROUP STATISTICS

	Troponin value	N	Mean	Std. Deviation	Std. Error Mean
	less than 0.6	29	.4163	.12311	.02286
	above 0.6	22	1.0464	.40156	.08561

	Levene's Test for Equality of Variances					
	F	Sig.	T	Sig. (2-tailed)	95% Confidence Interval of the Difference	
					Upper	Lower
TroponinT	32.817	.000	7.991	**.00006***	.78846	.47157

*significant at 0.05 level

ASSOCIATION BETWEEN CHARACTERISTIC VARIABLES AND TROPONIN T VALUE:

S. No	Variables	Troponin T (ng/ml)		Total	Chi-square value	P value
		≤ 0.6	**> 0.6**			
1.	**Total cross clamp time**					
	< 70	8	19	27	4.268	**0.039***
	> 70	14	10	24		
2.	**CPB time**					
	< 90	9	0	9	8.291	**0.004***
	> 90	20	22	42		
3.	**LTOC**					
	< 25	5	0	5	4.205	**0.040***
	> 25	24	22	46		
4.	**ATOC**					
	< 25	13	7	19	0.888	0.346

	> 25	16	15	31		
5.	**NO. of CP**					
	< 2	17	14	31	0.132	0.716
	> 2	12	8	20		
6.	**Post OP support**					
	Nil	6	9	15	9.009	**0.011***
	Minimal/Intermediate	22	8	30		
	High	1	5	6		
7.	**Duration of post OP support**					
	< 2 days	23	14	37	0.002	0.964
	> 2 days	6	8	14		
8.	**Requirement of IABP**					
	No	28	22	50	0.774	0.379
	Yes	1	0	1		
9.	**Post OP failure**					
	No	25	15	40	3.659	0.056*
	Yes	4	7	11		
10.	**Post OP EF score**					
	< 50 %	12	0	12	11.905	**0.001***
	> 50 %	17	22	39		
11.	**Mortality**					
	No	29	20	49	2.744	0.098
	Yes	0	2	2		

*. The Chi-square statistic is significant at the 0.05 level

From the above table, the following impressions are obtained.

1. The duration of cross clamp time has significant positive correlation with Troponin-T levels (p value 0.039)
2. The duration of CPB also has significant positive correlation with Troponin-T (p value 0.004)
3. Longest Time Off Cardioplegia has significant correlation with elevation of Troponin-T (p value 0.040)
4. High Troponin-T levels has significant correlation with Requirement of high doses of inotropes (p value 0.011)
5. High Troponin-T levels are associated with reduced Ejection Fraction in the postoperative period (P value 0.001)

LIMITATIONS OF THE STUDY:

1. Total number patients studied is less.
2. It is not a randomized controlled study.
3. Patients were operated by different surgeons and different surgical units. Different surgical units may have different approach in postoperative management, for example, early extubation versus late extubation, inotropic supports initiation and weaning, etc.,
4. Two patients had trans-septal approach (through right atrium) for mitral valve replacement. These two patients had De Vega annuloplasty in addition to MVR. Their Troponin-T values were 1.390 and 1.080 ng/ml. In this surgical approach, an additional incision is made in the inter-atrial septum. The cause for highly elevated values may be due to two incisions (right atrium and septum) and may

also be due to excessive retraction or due to the additional procedure (De Vega annuloplasty).

5. One patient had two incisions in the heart. MVR was done through left arial incision. Right atrium was then opened to perform De Vega annuloplasty. This patient's Troponin-T was 0.566 ng/ml.
6. One patient had prolonged hospital stay (30 days) and her Troponin-T value was 0.871 ng/ml. But the reason for her prolonged hospital stay was due to sternotomy wound infection. This is a confounding factor in the variable.
7. One patient had failed PTMC and subsequently taken up for surgery. It is not known whether PTMC causes elevation of Troponin-T, but MVR surgery was done only after 1 month. Hence, the previously attempted PTMC is unlikely to influence the results of Troponin-T values. Her Troponin-T value was 0.430 ng/ml.
8. One patient died on 5th post-operative day. Postoperative echo showed moderate to severe aortic regurgitation (preoperative echo showed only mild AR). This may be due to unmasking of AR by improved hemodynamics after MVR surgery. The patient's Troponin-T value was 1.570 ng/ml.
9. Two patients had adherent left atrial clot. They underwent clot removal and left atrial exclusion done by internal circumferential sutures with 4-0 prolene. The clot removal process or LAA exclusion procedure may be additional sources of Troponin-T elevation. Their Troponin-T values were 0.668 and 0.499.
10. One patient underwent partial maze procedure for atrial fibrillation (using electrocautery). Her Troponin-T value was 0.517 ng/ml.

DISCUSSION

Though this study was done with limited number of patients, it clearly shows that prolonged cross clamp time is associated with elevated Troponin-T values and that elevated Troponin-T values are associated (significant association) with increased morbidity in the form of prolonged ventilatory support, prolonged inotropic support, requirement of high doses of inotropes, postoperative cardiac failure and poor ventricular ejection fraction.

The per-operative variables that are associated (significantly) with high levels of Troponin-T are 1. Prolonged cross clamp time (more than 70 minutes), 2. Prolonged CPB time (>90 minutes) and 3. Prolonged CP time (>25 minutes between 2 cardioplegia doses).

By ROC curve analysis, the cut-off value of Troponin-T, was derived, above which the morbidity is significantly increased. The cut-off value is 0.6 ng/ml. (In a study conducted by Bernard l. Croal et al, with 1365 patients, and published in "*Circulation*" Journal, 2006;114:1468-1475, the cut-off value derived by ROC curve analysis, was 0.46 ng/ml and it was proved that the mortality significantly increased above this value).[14]

In this study, Troponin-T levels show good correlation with aortic cross clamp time, CPB duration and prolonged CP interval as well as postoperative variables like prolonged inotropic supports, high dose inotropes, prolonged ventilation and reduced LV function (poor EF). Hence, it is clear that Troponin-T is a good tool to assess the adequacy of myocardial protection.

CONCLUSION

Troponin-T is a reliable indicator of extent of myocardial injury in cardiac surgical patients and is a good armamentarium in the pool of diagnostics in cardiothoracic surgical field.

This test should be used more often than now, in postoperative period, to assess the adequacy of myocardial protection. This will have two important implications.

1. In an individual patient, who is hemodynamically unstable in the postoperative period, this test is helpful, in defining the cause of it.
2. The efficiency of different techniques of myocardial protection may be compared with one another, based on Troponin-T levels.

INTRODUCTION

Cardiac surgery is often complicated by some degree of myocardial ischemic damage, despite much improvement in myocardial protection strategies and surgical techniques. But, precise markers that can easily and specifically identify and quantify the extent of such damage is lacking. Electrocardiographic changes are of limited value in the perioperative period. Trans-esophageal echocardiography may be helpful in assessing left ventricular function and regional wall motion (which are indirect indicators of adequacy of myocardial protection) but it lacks the sensitivity to detect subtle degrees of myocardial damage. But, it is very essential to identify perioperative myocardial injury and its extent because it directly affects postoperative outcome. Further, the assessment of such injury is helpful to compare different methods of myocardial protection and will be useful in perioperative management of patients.

The development and availability of Troponin assays are considered to be one of the most important innovations in the past decade in cardiac diagnostics. Cardiac troponins (Troponin-T and Troponin-I) are proteins that are present in the thin filaments of myofibrils. They are released into the circulation whenever there is myocardial damage. Cardiac

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Assignment title	Medical
Author	Jothillingam Nallathambi 18101001 N/A Cardio Thoracic Surgery
E-mail	drjothilingam@gmail.com
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