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STUDY OF ADEQUACY OF MYOCARDIAL PROTECTION WITH CARDIOPLEGIA SOLUTION IN PATIENTS UNDERGOING CARDIAC SURGERY USING CPK-MB AS BIOMARKER

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ABSTRACT

Aim: To study the adequacy of myocardial protection with cardioplegia solution in patients undergoing cardiac surgery using CKMB as biomarke. Cardioplegia is the intentional and temporary cessation of cardiac activity primarily for cardiac surgery. Acting as perfusion agent, cardioplegia solutions can alter or inhibit ischemic injury by virtue of hypothermia and asystole. CPK-MB is the most sensitive and the most specific indicator available for the diagnosis of an acute myocardial infarction during the surgery which asseses adequacy of cadioplegia. Materials and Methods: This prospective analytical study was conducted in the department of Cardiothoracic and Vascular Surgery , Pushpagiri Medical College Hospital, Thiruvalla . All patients who were willing to participate in the study were briefly explained about the study procedure. Approximately 60-65 patients will be taken into consideration. Blood sample (residual) of 3ml is required which is obtained from the laboratory and CPK-MB level is estimated 6th and 12th hourly after administration of cardioplegic solution. The patients are selected based on inclusion and exclusion criteria. The level of biomarker can be analysed by using semi auto analyzer. The results obtained from the study can be compared with the normal range of CPK MB in blood. Follow up will be conducted during the study period. Results: Out of 70 patients evaluated, 65 patients was found to have a safer CK-MB ratio level(0-5%) . Comorbidities were compared with CK-MB level at 6th and 12th hourly and was found that diabetic patients with HTN shows comparitively higher average CKMB value. Other than 5% of those patients having higher CK-MB level ,postoperative QOL of 95% In addition, cardioplegia solutions can be used to avoid reperfusion injury.. This review is designed to investigate the adequacy of cardioplegia solution in of patients was found to be increased (p value<0.05).

Keywords – Coronary artery bypass grafting, Cardioplegia, Myocardial protection, Ischemia, Bloodless field, Hypothermia.

1. INTRODUCTION

Coronary Artery Bypass Graft (CABG) is a surgical procedure in which one or more blocked coronary arteries are bypassed by a blood vessel graft to restore normal blood flow to the heart . These grafts usually come from the patient's own arteries and veins located in the leg arm or chest[1].

Cardioplegia is intentional and temporary cessation of cardiac activity, primarily for cardiac surgery. The word cardioplegia combines the Greek cardio meaning the "heart", and *plegia*"paralysis". Technically, this means arresting or stopping the heart so that surgical

procedures can be done in a still and bloodless field. This process protects the myocardium, or heart muscle, from damage during the period of ischemia.

Cardioplegic solution: Cardioplegic Solution is a sterile, non pyrogenic, essentially isotonic, formulation of electrolytes in Water for Injection, USP. It contains Calcium Chloride Di hydrate, Magnesium Chloride hexa hydrate, Potassium Chloride and Sodium Chloride.

It is a "core solution" intended for use only after addition of sodium bicarbonate to adjust pH prior to administration. After buffering with sodium bicarbonate it is suitable for cardiac instillation (usually with hypothermia) to induce arrest during open heart surgery. Other agents may be added to the solution prior to instillation.

Cardioplegic solution with added sodium bicarbonate when cooled and instilled into the coronary artery vasculature, causes prompt arrest of cardiac electromechanical activity, combats intracellular ion losses and buffers ischemic acidosis. When used with hypothermia and ischemia, the action may be characterized as cold ischemic potassium-induced cardioplegia.

Calcium (Ca++) ion in low concentration is included in the solution to maintain integrity of cell membrane to ensure that there is no likelihood of calcium paradox during reperfusion.

Magnesium (Mg++) ion may help stabilize the myocardial membrane by inhibiting a myosin phosphorylase, which protects adenosine triphosphate (ATP) reserves have been shown to be additive.

Potassium (K+) ion concentration is responsible for prompt cessation of mechanical myocardial contractile activity. The immediacy of the arrest thus preserves energy supplies for post ischemic contractile activity in diastole[2, 3].

CPK- MB is a cardiac marker used to assist diagnosis of an acute myocardial infarction . CPK- MB test measures the blood levels of CPK-MB, the bound combination of two variants (isoenzymes CKM and CKB) of enzyme phospocreatine kinase. The test detects different isoforms of B subunit specific to myocardium and presence of cardiac related isoenzyme dimmers. Higher levels of CPK MB indicate the presence of myocardial damage [4].

S. Nair *et al* (2012) conducted study on "Effect of cardiopulmonary bypass on tissue injury markers and endothelial activation during coronary artery bypass graft surgery". The aim of this prospective study was to evaluate the influence of the technique of surgery on various tissue injury markers and the extent of endothelial activation in patients undergoing CABG and OPCAB coronary revascularization[26]. Bjorn Braathen*et al* (2009) conducted study on "Cold blood cardioplegia reduces the increase in cardiac enzyme levels compared with cold crystalloid cardioplegia in patients undergoing aortic valve replacement for isolated aortic stenosis". In this study, only in the group of patients receiving cold crystalloid cardioplegia was there a positive correlation between cardiac enzyme levels and cross clamp time[30]. Kenneth W Mahaffey *et al* (2007) conducted study on "Creatine kinase-MB elevation after coronary artery bypass grafting surgery in patients with non-ST-segment elevation acute coronary syndromes predicts worse outcomes: results from four large clinical trials". The aim is to assess the significance of creatine kinase (CK)-MB elevations in outcomes of patients with nonST-segment elevation acute coronary syndromes (NSTE ACS) who have undergone coronary artery bypass grafting (CABG) surgery. Conclusion: CK-MB elevations after CABG are independently associated with increased risk of mortality in patients with NSTE ACS[27]. Noel R Lamorena*et al* (2007) conducted study on "Evaluation of cardiac markers for ruling out Myocardial Infarction after Coronary Artery Bypass Grafting in patients". This study was conducted to evaluate the value of serum Troponin T and CK-MB concentrations for ruling out perioperative myocardial infarction (PMT) early after cardiac surgery. From this study, for ruling out PMI at RR after CABG, CK-MB is a better marker than Troponin T during the first 8 hrs after arrival at the recovery[28]. Newall *et al* (2006): conducted study on "Intermediate and high peri-operative cardiac enzyme release following isolated coronary artery bypass surgery are independently associated with higher one-year mortality". Conclusion: Cardiac enzyme release following CABG is associated with increased one-year all-cause mortality. The definition of peri-operative myocardial infarction following CABG should include elevation of CK-MB three or more times the upper limit of normal[29].

2. METHODOLOGY

Study Design was prospective study. Patients undergoing coronary artery bypass graft surgery were taken from Department of cardiothoracic and vascular surgery at Pushpagiri Medical College Hospital, Thiruvalla, Kerala**.** Time duration was 6 months. Approximately 70 patients undergoing bypass surgery. Follow up will be conducted during the study period.

2.1 Inclusion Criteria

- Both male and female patients.
- Patients on all age group
- Patients undergoing open heart bypass surgery under arrested heart.

2.2 Exclusion criteria

- Intra operative mortality
- Internal cardiac massage during surgery.
- Patients having defibrillation.
- Patients with congenital abnormalities in heart.
- Beating heart surgery.

2.3 Ethical Consideration

The study was started after getting the approval from the Institutional Ethics Committee. Informed consent was obtained from all patients who met with the inclusion criteria before commencing the study.

2.4 Brief Procedure of the study

A prospective study on "The adequacy of myocardial protection with cardioplegia solution in patients undergoing cardiac surgery using CPKMB as biomarker" was conducted in the department of Cardiothoracic and Vascular Surgery,Pushpagiri Medical College Hospital, Thiruvalla after getting approval from Institutional Ethics Committee.

All patients willing to participate were given a brief introduction regarding the study and the confidentiality of data.70 patients were taken into consideration and were selected based on inclusion and exclusion criteria. A written informed consent was obtained from the patients or caregiver and confidentiality of the data was maintained throughout the study. Patients who were undergoing CABG were taken and their hospital record was studied. A well designed data collection form was used to collect information.The statistical analysis was carried out using SPSS Version 11.5-computer software .

2.5 Collection of residual blood samples

About 3 ml of residual blood, which is obtained after the routine blood analysis, was collected from the Biochemistry lab. Blood was not withdrawn directly from the patient and any financial burden was not imposed on the patient. The collected residual blood was analyzed to estimate CPK-MB level 6^{th} and 12^{th} hourly after administration of cardioplegic solution using semi autoanalyser in the Pushpagiri College of Pharmacy. The results obtained from the study were compared with the normal range of CPK MB and CPK in blood.

2.6 Procedure to find CK-MB

2.6.1 Preparation of working reagent

The contents of one bottle of 2 CK-MB (Enzymes- activator) were dissolved in 1.1 ml of 1 CK-MB (Buffer-Antibody). The reconstituted reagent was kept for 15 minutes.

2.6.2 Determination of CK- MB values

1ml of reconstituted reagent was pipetted into a test tube, to which 0.05ml of blood sample is added. Auto analyzer was adjusted to: type of reaction - kinetic, wavelength 340 nm, flow cell temperature 37^0 C, interval as 30 sec and zero setting with distilled water. Then

the sample was aspirated in the semi- auto analyzer and read first absorbance of test at 300 sec and thereafter at 30, 60, 90, & 120 sec at 340nm. Determine the mean change in the absorbance per min.

3. RESULTS AND DISCUSSION

3.1 Analysis-1

Table 1: Distribution of CK-MB ratio with age

AGE	CK-MB			
	0-2%	2-5%	5-7%	MORE THAN 7
40-50	5	5	0	0
50-60	13	9	0	3
60-70	11	12	0	2
70-80	5	5	0	0

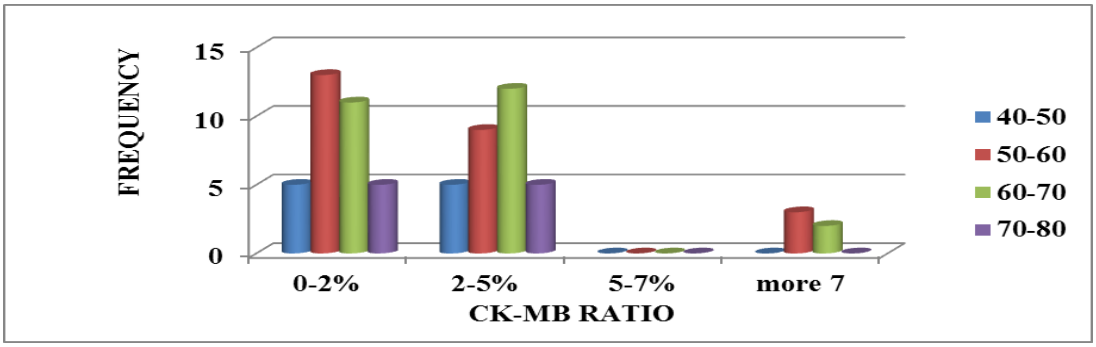

Fig. 1 : Distribution of CK-MB ratio with age

From the above table it was found that most of the patients fall in the safer range between 0-5% and only a few fall outside the safer zone (more than 7%). From this we can conclude that by administering cardioplegia solution, the patients risk of developing MI is reduced .

Table 2 : Distribution of CK-MB based on co-morbidities

DISEASE	CKMB	
	6TH HRLY	12TH HRLY
DIABETES (DM)	53.4	53.12
HYPERTENSION (HTN)	55.04	47.15
HYPERTENSION + DIABETES	61.04	55.4

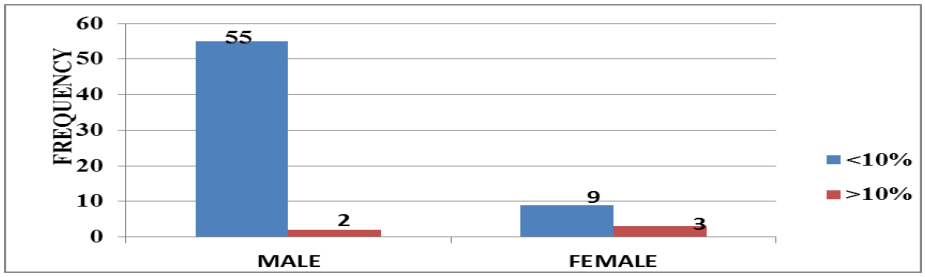

Fig. 2: Distribution of CK-MB based on co-morbidities

3.2 Analysis-2

Above graph shows that if the patient is having Diabetes along with Hypertension, have greater risk of developing rise in CK-MB.

Table 3 : Distribution based on CK-MB ratio and QOL

	QOL		
CK-MB RATIO	LESSTHAN 50	50-70	ABOVE 70
0-2%	0	14	20
2-5%	0	9	22
MORE THAN 5%	5	0	0

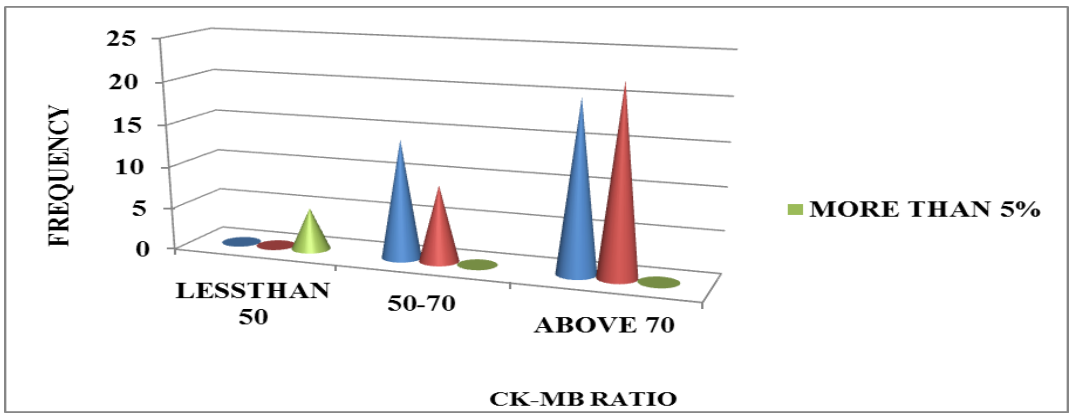

Fig. 3: Distribution based on CK-MB ratio and QOL

3.3 Analysis-3

From the table it was found that ,those 14 people who showed a QOL of 50-70 and 20 people of QOL of >70 belonged to group obtained a CKMB ratio of 0-2% . And taking CKMB ratio of 2-5%, 9 patients has QOL of 50-70 and 22 people has QOL >70. Patients who obtained CKMB ratio of >5% showed only QOL of less than 50 and they were 5.These observations prove that improved QOL is observed at a range of 0-5%.

Table 4: Distribution based on CK-MB to CK-NAC levels with gender

RANGE	MALE	FEMALE
<10%	55	9
>10%	2	3

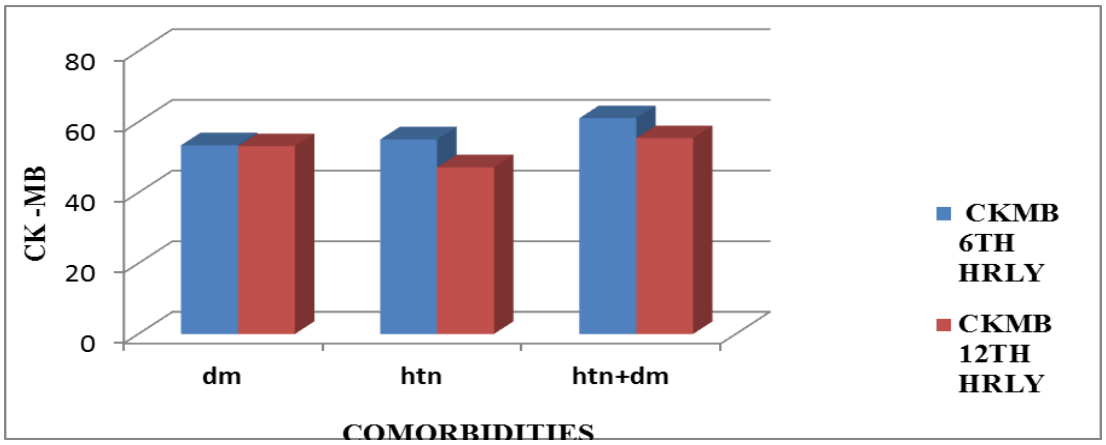

Fig. 4: Distribution based on CK-MB to CK-NAC levels with gender

3.4 Analysis-4

From above table it explains CK-MB levels for both male (55) and female(9) were below 5% and only 5 patients male (2) and female(3) were above 5% . thus concluding the patients are benefited from cardioplegia as there levels of CK-MB were in normal range.

Table 5: Comparision of CK-MB values with intial time of cardioplegic administration

	CKMB VALUE			
TIME OF ADMINISTRATION	0-2%	2-5%	5-7%	>7%
15-20	37	28	0	0
20-25	0	0	0	5

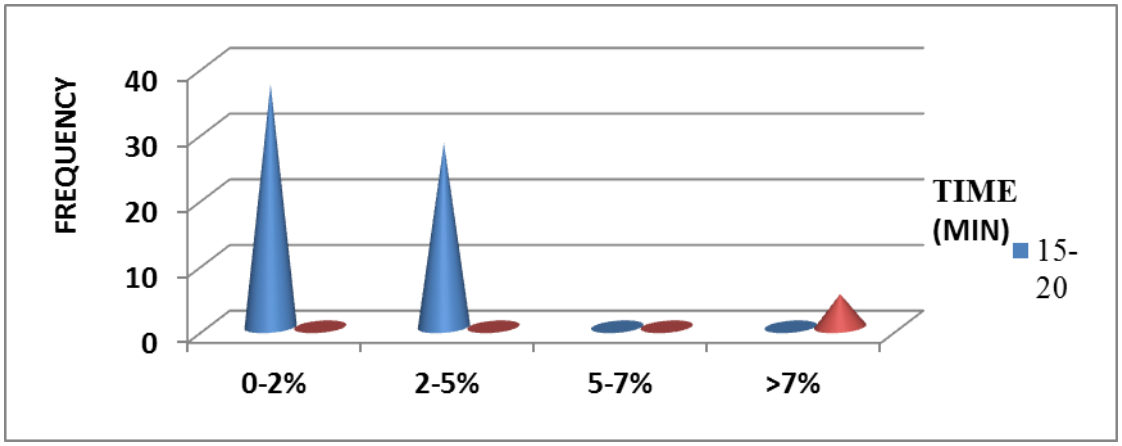

Fig. 5 : Comparision of CK-MB values with intial time of cardioplegic administration

3.5 Analysis-5

15-20 mins were taken by 65 patients for administration of initial time for cardioplegia and which is safest time for the administration. Only 5 patients were having initial time more than 20 min

Table 6: Distibution based on CK-MB

CK-MB	PERCENTAGE %	FREQUENCY
0-2%	50	35
2-5%	42.86	30
5-7%	0	0
More than 7	7.14	5

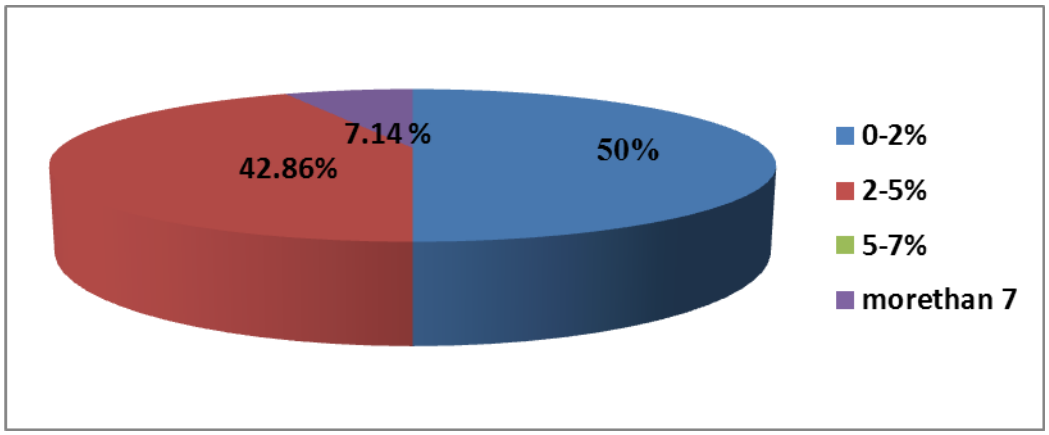

Fig. 6: Distibution based on CK-MB

3.6 Analysis - 6

From the table it was found that after cardioplegia administration, out of 70 patients, most of the patients have shown a safer CK-MB value (0-5%) indicating the reduced occurrence of MI due to proper cardioplegia administration.

3.7 Summary

- Gender: Total male patients were about 58(82.9%) and female were about 12(17.1%). 55 male and 9 female were having CK-MB below 5% and only 5 patients, (2 male and 3 female) were observed to be at 5%. Since those levels of CK-MB and CK-NAC were in normal range, we can say that the patients were benefited from cardioplegia .
- CK-MB ratio was also compared to gender and it showed the males (58) were having safer ratio than female (9).
- Co-morbidites: Total diabetes patient were found to be 9(12.8%), hypertension 25(35.70%) patients, and hypertension with diabetes were 30(51.40%). When the co-morbidites were compared with both 6^{th}hrly and 12^{th}hrly levels of CK-MB value, values of patients with diabetes and hypertension were found to be raised as compared to diabetes and hypertension alone.
- Coming to the first objective, To assess the need of cardioplegic solution in patients undergoing CABG and to assess the quality of life. During the surgery, due to variation in time interval of cardioplgia administration, the CK-MB levels rises. But at 12^{th}hrly the perfusion rates are been increased so CK-MB levels becomes normal.From the correlation it is shown that there is no relation between CK-MB and QOL. i.e they are inversely proportional, so the null hypothesis is rejected .
- Second objective was to assess the relationship between time taken for administration of cardioplegia and the level of CK-MB.Normal time interval for administering cardioplegia during surgery is 15-20mins. If there is a variation in the time-interval of cardioplegia administration, the CK-MB level starts rising indicating MI. Here 65 patients received cardioplegia at an interval less than 20 mins and 5 patients received cardioplegia at an interval between 20 & 30 min. It shows that most of patients who were administered with cardioplegia (15-20 mins interval) were benefited with myocardial protection accepted with a significant value p=0.05
- Third objective was to compare between the CK-MB to CK-NAC with gender and it was found that for 55 males and for 9 females the level of CK-MB to CK-NAC is below 10% and for 2 males and 3 females CK-MB values are above 10%. So majority of patients lies under range (below 10%) hence cardioplegia has proved to be potent.
- And the last objective was to find out the extent of risk of myocardial ischemia in patients with CAD, the patients having hypertension with diabetes showed higher values of CK-MB, so such patients are more prone to myocardial ischemia as compared to diabetes and hypertension alone.
- After the administration of cardioplegia, CK-MB increase was seen at 6^{th} hr, but at 12th hr substantial decrease in levels of CK-MB were observed there by knowing the fact the patients were getting good effect from the cardioplegia solution.

4. CONCLUSION

Cardioplegia is an important technique to protect the heart for safe conduct of complex surgeries like CABG . In the current study, safety and effectiveness of using cardioplegia in CABG was analyzed. For the assessment of safety, CKMB is compared with CK NAC and those CK MB values less than 10% of CK NAC was found to be safe . In the current study conducted on CABG patients in Pushpagiri Medical College Hospital, Tiruvalla, it was found that after cardioplegia administration, most of the CKMB values obtained was less than 10% of CK-NAC indicating that patients are not subjected to any further risk like MI .Thus mortality and morbidity was decreased raising the quality of life. In conclusion, our study depicts that the use of cardioplegia during CABG was found to be safe and effective for the patient.

REFERENCES

1) www.wikipedia.org/wiki/ coronary artery bypass surgery.
2) www.wikipedia.org/wiki/cardioplegia.
3) www.Drugs.com/ cardioplegia
4) emedicine.medscape.com/creatinine kinase.
5) Roger Walker and Cate Whittlesea. Clinical Pharmacy and Therapeutics. 2012, 5: 312.
6) R.R. Chatrath, T.K. Kaul and D.R. Walker. Myocardial protection during cardioplegia in open-heart surgery: a review. Canadian Anaesthetists' Society Journal.1980. 27(4): 381-382.
7) www.nhsc.com/ patient care/ conditions and treatment of CAD
8) www.hopkinsmedicine.org/healthlibrary/conditions/adult/cardiovascular diseases/coronary heart disease
9) Dee R. Who Assisted Whom? Tex Heart Inst journal.2003. 30(1):90
10) Jordan D. Haller, Andrew S, Olearchyk. Tex Heart Inst Jounal. 2002. 29(4):342-344.
11) Gleen P.et al.Cardiac pulmonary bypass : Principles and practice.2008 .3:172-187.
12) Sydzyik RT *et al.* Evaluation of a new generation cardioplegia administration system. journal of extracorporeal technology 1997 .29(3):145-153
13) Mourad JJ *et al*. Is hypertension a tissue perfusion disorder ? Implications for renal and myocardial perfusion .J HypertensSuppl 2006 .24(5):S10 –S16.
14) StruijkerBoudier HA *et al*. The heart, macrocirculation and microcirculation in hypertension:a unifying hypothesis. J HypertensSuppl .2003.21(3):S19-S23.
15) Jasinski M *et al*.Comparison of retrograde Vs antegrade cold blood cardioplegia: randomized trial in elective coronary artery bypass patient . Eur J Cardiothorac Surg.1997, 12(4): 620-626.
16) Onorati F *et al* .Does antegrade bloodcardioplegia alone provide adequate myocardial protection in patients with left main stem disease? J thoraccardiovascSurg 2003 .126(5):1345-131
17) Talwalkar N.G *et al*. Can retrograde cardioplegia alone provide adequate protection for valve surgery? Chest Journal 1999.115(1):135-139
18) Carrier M Pelletier LC ,Searle NR. Does retrograde administration of blood cardioplegia improve myocardial protection during first operation for coronary artery bypass grafting? Ann Thorac Surg1997;64(5):1256-1261
19) Louagie YA *et al*. Continuous cold blood cardioplegia improves myocardial protection: a prospective randomized study .Ann ThoracSurg .2004.77(2):664-671.
20) Borger MA ,Rao V *et al*.Retrospective coronary bypass surgery:effect of patent grafts and retrograde cardioplegia.JThorac Cardiovasc Surg 2001;121(1):83-90.
21) Yau TM *et al*. Changing patterns of reoperative coronary surgery: trends in 1230 consecutive reoperations.JThorac Cardiovasc Surg 2000.120(1):156-163
22) Gundry SR *et al*. Optimal delivery of cardioplegic solution for "redo" operations.JThorac Cardiovasc Surg .1992.103(5);896-901.
23) Hayashi Y *et al*. Controlled nicorandil administration for myocardial protection during CABG under cardiopulmonary bypass. Journal of Cardiovasc Pharmacol. 2001.38(1): 21-28.
24) Faisal A. Mourad *et al* .Myocardial protection during CABG: Warm blood versus coldcrystalloid cardioplegia, is there any difference? Journal of the Egyptian Society of Cardio-Thoracic Surgery. 2016. 24:215-222.

25) Helene De Bruyn et al. Myocardial Protection during Cardiac Surgery: Warm Blood versus Crystalloid Cardioplegia. World Journal of Cardiovascular Diseases. 2014. 4:422-431.

26) S. Nair, k. Iqbal, M. Phadke, UE Jadav, J Khandekar, JMS Khandeparkar. Effect of cardiopulmonary bypass on tissue injury markers and endothelial activation during coronary artery bypass graft surgery. Journal of Post graduate medicine. 2012.58(1): 8-13.

27) Kenneth W. Mahaffey, Mathew T Roe, Rakhi Kilaru, Robert A Harrington. Creatine kinase-MB elevation after coronary artery bypass grafting surgery in patients with non-ST-segment elevation acute coronary syndromes predicts worse outcomes: results from four large clinical trials. European Heart Journal.2007.28 (4): 425-32.

28) Noel R. Lamorena, Santos Jose G. Abad. Evaluation of Cardiac Markers for Ruling Out Myocardial Infarction After Coronary Artery Bypass Grafting in Patients. Adult cardiology. 2007. 105- 108.

29) N Newall,AY Oo, ND Palmer, AD Grayson ,TJ Hine ,RH Stables ,BM Fabri, DR Ramsdale. Intermediate and high peri-operative cardiac enzyme release following isolated coronary artery bypass surgery is independently associated with higher one-year mortality. Journal of Cardiothoracic Surgery. 2006. **1**:20.

30) Bjorn Brathen *et al*. Cold blood cardioplegia reduces the increase in cardiac enzyme levels compared with cold crystalloid cardioplegia in patients undergoing aortic valve replacement for isolated aortic stenosis; The journal of vascular and thoracic surgery;2009 ;139(4);874-880.