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To study the myocardial oxygen extraction from cardioplegic solution as a predictor of postoperative outcome in valvular replacement surgeries of heart.

Running title: Myocardial oxygen extraction as a predictor of postoperative outcome.

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Abstract:

Introduction: During cardiac surgery with heart arrested and aortic cross clamp on, heart suffers a variable degree of ischemia, and thus myocardial oxygen extraction (MOE) also varies with each cardioplegic dose. Does MOE have any bearing on postoperative outcome and can it be a reliable predictor of same?

Aims: To study the myocardial oxygen extraction as a predictor of postoperative outcome in valvular replacement surgeries of heart.

Materials and methods: 66 consecutive cases of valve replacement surgeries were included. Ischemic heart disease was ruled out in all. During surgery, Oxygen content of cardioplegic dose was ascertained at the aortic root and at coronary sinus, and MOE was calculated. Cases were divided into two groups: those with MOE more than 25ml% and others with less than 25ml%. Postoperative outcome was noted in each, viz a viz complications, hospital and ICU stay, morbidity and mortality. Statistical correlation was drawn.

Results: In general, those with MOE higher than 25ml% had a better outcome, marked by significantly less complications, ICU and hospital stay and mortality. While as those with less than 25ml% had a worse outcome in similar parameters.

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Conclusion: Though high MOE was associated with a better postoperative outcome, more studies with bigger sample size need to be undertaken to validate the findings and establish MOE as a predictor of postoperative outcome.

Key words: Myocardial oxygen extraction, cardioplegia, complications, ICU stay

Introduction

During open heart surgery, the heart, with aorta cross clamped, suffers a variable degree of ischemia, despite the attempts at minimizing the metabolism by achieving cardioplegic arrest and cooling the heart to variable degree of hypothermia[1]. During cardioplegic reperfusion, every heart extracts oxygen at constant ratio at a given load; but may vary from heart to heart depending upon the status of myocardium[2]. We intend to study the effect of this myocardial oxygen extraction (MOE) during cardioplegic reperfusion on the postoperative outcome, with respect to complications, ICU and hospital stay and mortality. Or more precisely, to study the MOE as a predictor of postoperative outcome. Our search in the available database did not reveal a single study which directly studied MOE as a predictor of postoperative outcome, though a few of the studies touch the concept which would be discussed in later part of this manuscript.

Heart is an obligate aerobic organ; it depends on a continuous supply of oxygen to maintain normal function. Myocardial oxygen reserve is exhausted within 8 seconds after the onset of normothermic global ischemia. A unique aspect of myocardial energetics is that 75% of the coronary arterial oxygen presented to the myocardium is extracted during a single passage through the heart despite a wide range of cardiac workloads [3]. The oxygen saturation, and hence the oxygen content, of the coronary venous blood is the lowest in the body, due to the very high (~0.6) myocardial oxygen extraction ratio. Therefore, the heart is susceptible to the limitations of oxygen delivery, whereby an increase in myocardial oxygen consumption can be met only by augmentation of coronary blood flow, as there is not much ability to increase the oxygen extraction during conditions of reduced supply. This makes the myocardial tissue vulnerable to ischemia.[4] The oxygen extraction ratio (O_2ER) is the fraction of the arterial oxygen content that is consumed as the blood traverses the organ or tissue. It is determined by dividing the difference of the arterial and venous oxygen content by the arterial oxygen content. The normal O_2 ER is only 0.2–0.3 indicating a significant excess of oxygen being delivered to the tissues. This excess allows for a cushion should oxygen delivery be compromised, thereby, minimizing the need for anaerobic metabolism.

In cardiac surgery, a marked increase in coronary blood flow is observed at the beginning of the reperfusion period, after the aortic clamp is removed.[5,6] This is consequent to a variable degree of ischemia that affects myocardium during cardioplegic arrest. Hence myocardial extraction may vary from heart to heart with each dose of cardioplegia given, which in turn would be determined by duration of cardioplegic arrest, temperature of heart, underlying coronary artery disease or ischemic cardiomyopathy. In our study, we aim to see the correlation between the myocardial oxygen extraction and the post-operative outcome in valvular heart surgeries.

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Material and Methods

The study was conducted in the Department of Cardiovascular and Thoracic Surgery, Sher-i-Kashmir Institute of Medical Sciences, Srinagar (India). The study was prospective in nature and 66 cases were studied. The informed consent was taken from all cases enrolled for the study. Besides the routine workup, special investigations included echocardiography and coronary angiography if patient's age was >50 years. Any patient with suspicion or confirmed coronary artery disease was excluded.

We maintained the temperature of 28-32C^{o} in all patients during cardioplegic arrest. The pump flow rate was 2.8-3.2 L/minute. Myocardial oxygen extraction was calculated by taking blood samples from Antegrade/Retrograde cannula (Cardioplegic Blood) and simultaneously from the Coronary sinus/Coronary ostia and the determined oxygen content of the arterial and coronary sinus was used to calculate the myocardial oxygen extraction (ml %) by using equation:

Oxygen Extraction (ml of oxygen/100 ml of Blood) = $[(CaO_2 - CvO_2) \div CaO_2] \times 100$

CaO_2 is oxygen content of arterial or pump blood

CvO_2 is oxygen content of coronary sinus blood

Oxygen content = 1.36ml O_2/ g x Hb / 100ml x O_2 sat % +(0.003 x PO_2)

Patients were shifted to intensive care unit. Patients were divided into two groups, viz, Group 1 with less than 25ml Oxygen/100ml blood and Group 2 with more than 25ml Oxygen/100ml blood oxygen extraction. The data was recorded without error and was analyzed statistically. Thirty day mortality and morbidity was recorded.

OBSERVATION

The age range of our series of 66 patients was 20 years to 65 years with mean age of 36.5 (34 males and 32 females). Most common surgical approach was median sternotomy in 91%, the most common surgical procedure performed was DVR in 30.3% (Table 1). Valve pathology was Rheumatic in 78.8% of cases, and the most common prosthetic valve implanted was Chitra in 54.2%. The correlation of myocardial oxygen extraction [ml of oxygen/100 ml of blood(ml%)] with postoperative morbidity and mortality is drawn. As shown in Table 2, the postoperative morbidity and mortality were more

Surgery and Surgical approach	n	%
Median sternotomy	60	91.0
Partial sternotomy	4	6.07
Right thoracotomy	2	3.04
MVR	18	27.2
AVR	14	21.2
MVR Plus AV Repair	4	6.06
DVR	20	30.3
DVR plus TV Repair	10	15.1

Table 1: Surgical approach and Type of surgery in studied subjects

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Variable		MOE <25 N(%)	MOE>25 N(%)	Total	Mean±SD	P value
Bleeding	No	38(65.5%)	20(34.4%)	58	19.20±9.31	0.64
	Yes	6(75%)	2(25%)	8	20.29±5.49	
Arrythmia	No	18(52.9%)	16(47)	34	22.53±8.39	0.005*
	AF	24(80%)	6(20%)	30	16.30±8.41	
	Bradycardia	2(100%)	0(0.0%)	2	10.32±.000	
Sepsis	No	40(64.5%)	22(35.4%)	62	19.30±9.19	0.771
	Yes	4(100%)	0(0.0%)	4	19.75±1.87	
Mediastinitis	No	40(64.5%)	22(35.4%)	62	19.30±9.19	0.771
	Yes	4(100%)	0(0.0%)	4	19.75±1.87	
LCOS	No	40(64.5%)	22(35.4%)	62	19.30±9.19	0.771
	Yes	4(100%)	0(0.0%)	4	19.75±1.87	
Renal	No	36(62%)	22(37.9%)	58	20.66±9.12	0.01*
	ARF	8(100%)	0(0.0%)	8	14.00±4.79	
Cardiac	No	44(68.7%)	20(31.2%)	64	19.12±8.97	-
	CT	0(0.0%)	2(100%)	2	26.02±.000	
Pulmonary	No	37(62.7%)	22(37.2%)	59	19.52±9.35	0.063
	Pneumonia	3(100%)	0(0.0%)	3	14.99±2.61	
	ARDS	4(100%)	0	4	15.60±4.03	
Neurologic	No	42(65.6%)	22(34.3%)	64	19.56±8.95	-
	Hemiparesis	2(100%)	0(0.0%)	2	11.97±.000	
Others	No	41(67.2%)	20(32.7%)	61	19.27±9.12	0.379
	Reoperation	1(33.3%)	2(66.6%)	3	24.62±2.42	
	Tracheostomy	2(100%)	0(0.0%)	2	13.32±0.00	
Outcome	Survived	40(64.5%)	22(35.4%)	62	19.30±9.19	0.771
	Death	4(100%)	0(0.0%)	4	19.75±1.87	

Table 2: Correlation of MOE [myocardial oxygen extraction, ml of oxygen/100 ml of blood (ml%)] with postoperative morbidity and mortality in studied subjects. AF=Atrial Fibrillation, LCOS=Low cardiac output syndrome, ARF=Acute renal failure, CT=Cardiac tamponade, ARDS=Adult respiratory distress syndrome

common in patients with myocardial oxygen extraction less than 25 ml %. Arrhythmias and renal failure was significantly higher in group with MOE less than 25ml%

Correlation of myocardial oxygen extraction (ml%) with Intensive care unit stay and total hospital stay: The ICU and hospital stay was more in patients with myocardial oxygen extraction less than 25 ml% (Table 3). Both the parameters showed statistically significant correlation with MOE (Figure 1 & Figure 2).

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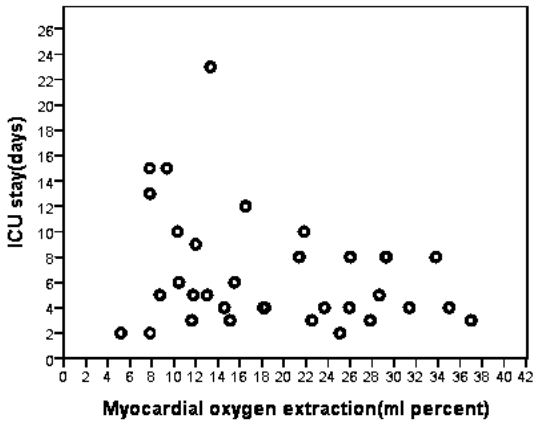

Fig.1 Scatter graph showing ICU stay (days) and myocardial oxygen extraction (ml%) in studied subjects with Pearson's Correlation coefficient (r=0.266, p=.031*)

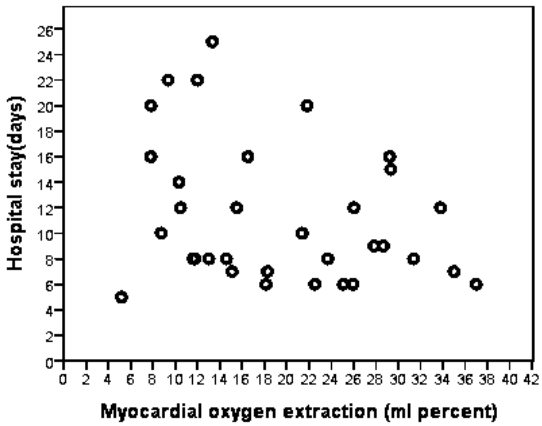

Fig.2 Scatter graph showing total hospital stay(days) and myocardial oxygen extraction (ml%) in studied subjects with Pearson's correlation coefficient (r=0.297, p=0.015*)

Discussion

We directly measured the MOE during cardiac arrest by using blood gas analysis of the blood in cardioplegic canula and that returning from the coronary sinus in an antegrade infusion, or from coronary ostia in retrograde cardioplegia. It is clear that myocardial metabolism is suppressed as myocardial temperature decreases. In our study, the suppression of myocardial oxygen consumption is considered to be secondary to cardiac hypothermia, which was induced by lower systemic temperatures and topical ice cooling of heart.

In our study most of the morbidity and mortality factors- bleeding, arrythmia, sepsis, mediastinitis, low cardiac output syndrome, acute renal failure, cardiac tamponade, stroke, reoperation, pulmonary complications, tracheostomy and death occurred in patients with MOE less than 25 ml% (Table 2). Among arrhythmia, atrial fibrillation occurred in 30 patients, 24 patients (80%) had MOE less than 25 ml% and 6 patients (20%) had MOE more than 25 ml %, bradycardia in 2 patients (p=0.005*). Hashemzadeh K et al.[7] reported postoperative atrial fibrillation in patients with intraoperative ischemic reperfusion injury, which the authors attribute to aortic cross clamp time with significant positive correlation; however, any relation with MOE is not discussed.

As mentioned earlier, we couldn't find a single research article in Pubmed, Cochrane Reviews, Wiley Online, SAGE or Google search engine which would study effect of MOE on postoperative outcome. There have been, though, a few studies about MOE during cardioplegia perfusion analyzing or comparing among various groups or even in animal models[8,9]. Whether or not the MOE can predict postoperative outcome remains to be established. Clinically, coronary artery disease is an established disease entity which would decrease myocardial oxygen extraction secondary to the hypoperfusion of myocardium, which leads to a poorer postoperative

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outcome. These cases were excluded from our study group. Is it the similar mechanism and biochemical effects involved during cardioplegia perfusion in group 1 (less than 25ml% MOE) of our study cohort that leads to worse outcome? And what are those factors, other than CAD, that affect MOE, and therefore likely show some correlation with MOE and postoperative outcome? Since temperature and type and interval of cardioplegia is same in all patient, left ventricular mass and insidious fibrillatory activity during cardioplegic arrest seem to be two factors relevant to MOE change.

LV Mass: Certain conditions like Aortic stenosis or mitral regurgitation are associated with LV hypertrophy and increased mass. Clinically significant hypertrophy is known to cause subendocardial ischemia in contracting heart. It has been observed[10] that if LV hypertrophy occurs in infancy, there is relative increase in microvascularity of myocardium so that myocardial blood flow index remains largely unchanged, same phenomenon is observed in athletes. However in adult pathological states, there is hypertrophy without concomitant augmentation of vascular channels, thereby leading to vulnerability to ischemia. With time there are permanent pathological changes in myocardium. Though flow index is reduced, but we don't know what happens to myocardial oxygen consumption. It is likely that pathological hypertrophied myocardium does not extract oxygen optimally so MOE is decreased in such hearts. Since during surgery, the LV wall tension, which is an important determinant of MOE, is excluded, the basal metabolic activity in hypertrophied myocardium is also decreased owing to above cited myopathic changes.

Fibrillatory arrest: though we didn't use fibrillatory arrest in any of our patients, but even in arrested hearts, some degree of fibrillation always takes place which may not be visible during surgery but is evident on ECG monitor. This usually happens as cardioplegic effects starts weaning off and/or due to unequal hypothermia of heart. There are studies[11,12] which suggest that empty, vented, non-distended fibrillating heart consumes same oxygen as beating empty heart. Distension of heart during "useless" contractility of heart leads to subendocardial ischemia unless the coronary perfusion pressure is sufficient to overcome it, much more so when no coronary flow is there during arrest. It is therefore imperative that empty vented heart with proper cardioplegic perfusion intervals will not have any change in MOE in presence of fibrillation. Given that more oxygen consumption does occur as compared to complete asystole, variable changes in MOE are expected in fibrillation if distension of chambers takes place. These variables such as degree and duration of fibrillation in supposedly asystolic heart, distension and subendocardial ischemia are immeasurable, so postoperative outcome secondary to it cannot be reliably correlated with MOE.

In our study, ICU stay was 7.39±5.14 days in 66.6% with MOE less than 25ml % and 5.18±2.30 days in 33.3% with MOE greater than 25 ml% (p=0.019*). Hospital stay was 12.27±6.06 days in 66.6% with MOE less than 25 ml% and 9.64±3.52 days in 33.3% with MOE greater than 25 ml% (p=0.03*). See Table 3 and Figure 1 & Figure 2.

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Variable	MOE (ml %)	N(%)	Mean	S.D	p value
ICU Stay(days)	Less than 25	44(66.6%)	7.39	5.14	0.019*
	Greater than 25	22(33.3%)	5.18	2.30	
Hospital Stay(days)	Less than 25	44(66.6%)	12.27	6.06	0.03*
	Greater than 25	22(33.3%)	9.64	3.52	

Table 3: Correlation of myocardial oxygen extraction, MOE (ml%) with ICU stay and hospital stay (days) in studied subjects

The results of this study indicate that globally ischemic myocardium is able to utilize more oxygen efficiently for restoration of its energy substrates and performs better as it recovers from the arrest, while the failure to efficiently utilize the oxygen during cardioplegic perfusion due to any reason doesn't predict at good outcome.

Limitations of the study: Limitation of this study is the small sample size, not enough to provide statistical power to the study. Besides the study has inherent and obligatory bias of not being randomized as per the statistical protocol.

Summary and conclusion

We infer from the statistical analysis of the study data that MOE and postoperative morbidity and mortality have a direct correlation. MOE less than 25 ml % was associated with high risk of postoperative adverse events and more than 25 ml % was associated with good surgical outcome. Further studies with large sample size, having statistical power, are needed to substantiate the claims of the study and provide insight in to the mechanism of our observations.

Conflict of interest: The Authors declare that there is no conflict of interest.

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