Clinical Study of Myocardial Protection: Comparison of Cold Blood Cardioplegia & Cold Crystalloid Cardioplegia in Mitral Valve Replacement

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Abstract. This article aims to assess the clinical outcome of two groups of patients by using cold blood cardioplegia and cold crystalloid cardioplegia for myocardial protection during the mitral valve replacement in open-heart surgical cases. Clinical data were collected from hospital records of the patients who underwent open-heart surgery for mitral valve replacement. 20 patients were divided into two groups. Group A included 10 patients treated with cold crystalloid cardioplegia used. Group B included 10 patients operated on where cold blood cardioplegia was used for myocardial protection. Data was analyzed in both groups by using the T-test for continuous variables. And Chi-Square Test was performed for categorical variables. There was no significant difference in cross-clamp time, bypass time in both groups. Use of cardioversion after declamping in Group A was 10% and 10% in Group B. Use of inotropic agents when CPB stop 90% in Group A and 50% in Group B. Mean duration of mechanical ventilatory support was 12.20 hours in Group A and 11.30 hours in Group B. Mean blood drainage was 1.651 ml in Group A and 1.492 ml in Group B. Use of inotropic agents to keep the systolic blood pressure > 100 mmHg was 60% in Group A and 80% in Group B. There was no significant difference in CK and CK-MB during and after the operation but there was a significant difference in Tn1 during surgery after 30 minutes of CPB. Different cardioplegia techniques and strategies have been demonstrated to be safe and useful in cardiac surgery. Cold blood cardioplegia provides myocardial protection better than cold crystalloid cardioplegia.

Key words: Crystalloid Cardioplegia, Blood Cardioplegia, Myocardial Protection, Cardiopulmonary Bypass, Open Heart Surgery

Introduction

Myocardial protection (MP) is the key for cardiopulmonary bypass (CPB) heart operation. MP during cardiac surgery aims to protect myocardial function at the same time as providing a bloodless and motionless operating field. Strategies on how to decrease or prevent post-ischemic myocardial dysfunction that occurs intra-operatively during cardiac surgery have been discussed for more than half a century (Bigelow, Lindsay, & Greenwood, 1950). First reported using hypothermia to decrease myocardial oxygen described the use of electromechanical cardiac arrest induced by potassium infusion, permitting cardiac surgery to be performed on a non-beating flaccid heart and clear surgical field (Melrose et al., 1955). The combination of both of these techniques has become the golden standard in MP during surgery until now, allowing surgery with outstanding clinical outcomes introduced a crystalloid solution into clinical practice at St. Thomas Hospital (Braimbridge et al., 1977). By the 1980s, blood-based potassium solutions were performed to further improvement of MP and to reduce myocardial enzymes release (Barner, 1991). Based on the theory that blood would be a superior and healthier delivery mean for its oxygenating and buffering capacity (Buckberg, 1979). Luckily, the majority of MP strategies now available do allow patients to undergo conventional and complex cardiac surgery with an operative mortality rate ranging from less than 2% to 4%.

In China, in 1958 successfully done the first case of open-heart surgery under CPB (Su, 1979). This led to quick progress on cardiac surgery procedures in China. Unluckily, the Cultural Revolution occurred from 1966 to 1976 in China, and research on cardiac surgery was

discontinued (Wan & Yim, 1999). In the past two decades, studies on MP have extensively enhanced all over China, with modification of medical instruments, such as the ECG and ECHO and the use of myocardium enzymes such as creatine kinase and troponin I or T to evaluate levels of myocardial injury (Ji et al., 2002; Li et al., 1999). We reviewed the published literature by Chinese investigators relating to the topic of MP during CPB, evaluated current techniques of MP aimed at improving the results of contemporary cardiac surgery, and summarized future perspectives of MP under investigation in China.

Cold Crystalloid Cardioplegia and Blood Cardioplegia

In China, early cardioplegic techniques employed cold crystalloid solutions to start and continue intra-operative cardiac arrest. Instead of crystalloid cardioplegia, cold blood cardioplegia was considered a clinical practice in Fuwai Hospital for adult patients in 1994 and provided an advantage more than cold crystalloid cardioplegia. Over 30 000 open-heart surgeries have been performed with cold blood cardioplegia from 1994 to 2006 in Fuwai Hospital. Based on a literature search, some results showed that blood cardioplegia provided better protection than crystalloid cardioplegia not only in adult patients but also in pediatric patients (Tan, Hu, & Zhou, 2005; Yuan et al., 1995).

Etiology of Mitral Valve Diseases

Valve disease may be acquired or congenital. Historically, the majority of mitral valve disease caused post-rheumatic but, with the cure of rheumatic fever (RF), this has reduced considerably. Systemic lupus erythematosus, atrial myxoma, rheumatoid arthritis, and bacterial endocarditis are the other causes of mitral valve diseases. The last typically occurs on pre-existing pathology. The common causes of regurgitation are myxomatous degeneration, connective tissue disease, ruptured chordae tendineae, the left ventricle dilatation including dilated cardiomyopathy, and RF. Only 50% of cases of typical rheumatic heart (RHD) disease are associated with an account of RF and many times heart lesions are not caused by RF. Pure mitral stenosis (MS) is highly indicative of RHD. RHD is diagnosed by an echocardiogram (ultrasound) (Reményi et al., 2012). Symptoms of mild RHD may not be noticed for many years (Zühlke et al., 2016).

Rheumatic Heart Disease & Causes

RHD is associated with damage to the valves of the heart. Rheumatic heart disease is a condition in which the heart valves have been permanently damaged by rheumatic fever. The heart valve damage may start shortly after untreated or under-treated streptococcal infection such as strep throat or scarlet fever. An immune response causes an inflammatory condition in the body which can result in ongoing valve damage. RHD is a complication of RF and typically occurs after attacks of RF. The occurrence of RHD has been significantly reduced by the widespread use of antibiotics which are very effective against the streptococcal bacterium that causes RF. Regular antibiotics are prescribed for people with RHD to prevent recurrent ARF and subsequent worsening of the valve damage (RHD Australia, ARF/RHD writing group, 2020). RHD develops after ARF and particularly with recurrent ARF.

Rheumatic fever (RF) is an inflammatory disease that is caused by Group A streptococcal infection, (such as scarlet fever or strep throat). Supposed to be following an antibody cross-reactivity which can involve the heart, skin, joints, and brain, the illness develops characteristically in two to three weeks after a streptococcal infection. Rheumatic fever can occur at any age but usually occurs in children ages 5 to 15 years old. It's rare in developed countries like the United States. The illness is so-called because of its resemblance in a presentation to rheumatism.

Who is at Risk for Rheumatic Heart Disease?

Untreated or under-treated strep infections can increase the risk for rheumatic heart disease. Children who get repeated strep throat infections are at the most risk for rheumatic fever and rheumatic heart disease.

Prevalence of Rheumatic Heart Disease in China

Rheumatic heart disease affected approximately 2 million middle-aged to elderly Chinese, thus constituting a significant health burden. Participants 9124 were interviewed, and 8652 fulfilled the questionnaires and underwent clinical assessment, 8080 participants done echocardiographic examinations. In this research work, 20–29-year-old females were the smallest age-gender group (7.8%), and 30–39-year-old males were the largest age-gender group (11.6%). Workers were the biggest occupational group (33%) and civil service employees were the second biggest (29.9%). In 8080 subjects, 7882 were from Han nationality (96.9%), 14 Hui (0.2%), 10 Man (0.1%), and 223 from other nationality (2.6%).

Fifteen subjects were recognized as having definite echocardiographic indication for RHD, together with 4 males and 11 females (Table 1). The prevalence of RHD was designed to be 186/100,000. The range of ages of these 15 subjects was 27–71 years and the mean age was 48.3 ± 13.1 years.

Table 1. Clinical features in the participants with rheumatic heart disease

No.	City	Age/sex	History	Symptoms	Murmur	ECG	Diagnosis
1	Zhengzhou	64/M	0	0	0	0	MS + MI
2	Shaoyang	30/F	8 years	+	+	0	MS + AI
3	Kuitun	49/F	2 years	+	+	0	MS + MI
4	Shaoyang	60/F	1 year	+	+	AF	MS + MI + TI
5	Jixi	50/M	5 years	0	0	AF	MS (replacement) + AI + TI
6	Shaoyang	51/F	26 years	+	0	0	MS
7	Shaoyang	35/F	9 years	+	+	P mitrale	MS + AI
8	Shaoyang	45/F	16 years	+	+	P mitrale	MS + MI + AI + TI
9	Jixi	49/F	0	0	0	AF	MS + MI + AI + AS
10	Nanning	27/M	0	0	+	0	MS + AI (mild)
11	Kuitun	30/F	0	0	0	0	MS
12	Zhengzhou	57/F	27 years	+	+	P mitrale	MS
13	Xi'an	58/F	38 years	+	+	0	MS + MI
14	Xi'an	48/F	0	0	0	0	MI + MS
15	Jixi	71/M	0	+	+	AF	MS + MI + TI

Note: M = male; F = female; MS = mitral stenosis; MI = mitral insufficiency; AI = aortic insufficiency; TI = tricuspid insufficiency; AS = aortic stenosis

In the 15 RHD patients, 6 were recognized for the first time having RHD diagnosed (40%), 9 had a history from 1 to 38 years of RHD (14.6 ± 13.0 years). All of them with mitral stenosis, 7 had mitral insufficiency, but only 9 with typical cardiac murmurs; 4 with atrial fibrillation, and 3 with electrocardiographic P mitral; 9 had identified heart failure (NYHA class ≥II).

Table 1 and Table 2 list the specific valve lesions detected by the survey. One patient was replaced of the mitral valve with a mechanical valve and this patient also had tricuspid and aortic insufficiency. 6 patients had aortic insufficiency, one of them was diagnosed with aortic stenosis.

Table 2. Echo-cardiographic findings in the participants with rheumatic heart disease

No.	City	Age/sex	LAD	LVD	RVD	EF (%)	Area of MV	Diagnosis
1	Zhengzhou	64/M	37	45	16	53	2.0 cm^2	MS + MI
2	Shaoyang	30/F	39	49	18	56	1.5 cm^2	MS + AI
3	Kuitun	49/F	38	52	17	57	1.3 cm^2	MS + MI
4	Shaoyang	60/F	42	48	18	59	0.9 cm^2	MS + MI + TI
5	Jixi	50/M	41	47	19	55	–	MS (replacement) + AI + TI
6	Shaoyang	51/F	40	46	15	53	1.5 cm^2	MS
7	Shaoyang	35/F	39	54	18	52	1.4 cm^2	MS + AI
8	Shaoyang	45/F	42	49	17	55	1.4 cm^2	MS + MI + AI + TI
9	Jixi	49/F	46	36	21	52	1.3 cm^2	MS + MI + AI + AS
10	Nanning	27/M	39	44	16	57	1.7 cm^2	MS + AI(mild)
11	Kuitun	30/F	43	55	16	54	1.5 cm^2	MS
12	Zhengzhou	57/F	46	48	18	54	1.8 cm^2	MS
13	Xi'an	58/F	42	49	16	52	1.2 cm^2	MS + MI
14	Xi'an	48/F	37	46	17	55	1.9 cm^2	MI + MS
15	Jixi	71/M	55	56	22	54	1.0 cm^2	MS + MI + TI

Note: M= male; F = female; LAD = left atrial diameter; LVD = left ventricular diameter; RVD = right Ventricular diameter; EF = ejection fraction; MV = mitral valve; MS = mitral stenosis; MI= mitral insufficiency; AI = aortic insufficiency; TI = tricuspid insufficiency; AS =aortic stenosis

In this retrospective research, we came to know that the prevalence of chronic RHD was 186/100,000 adults and 10 times higher than the prevalence in developed countries such as Canada (0.22/1000) and Japan (0.14/1000) (Rabkin & Chu-Chu-Lin, 1988). It is significant health trouble in China. It has long been recognized that incidence of acute RF and prevalence of RHD have declined since the 1950s, with healthier living standards and public health, but the true incidence of RHD was unknown until now. Over the past decades, the incidence of RHD was derived from school surveys or hospital discharges.

Between 1940 and 1983, it has been reported that the incidence of RHD varied from 1.8 to 11/1000 (average 6/1000), although between 1984 and 1995 the prevalence varied from 1 to 5.4/1000 (Schaffer et al., 2003). This present study is a population-based survey, which should provide a better assessment of the prevalence and severity of RHD. But RHD typically occurs in low-income families. Over-population and over-crowding, poor quality, and poor access to medical care are undoubtedly the risk factors for the high prevalence of RHD (Eisenberg, 1993).

Echocardiography is a comparatively new and cost-effective technique for screening RHD and quantifying the severity of RHD, the echocardiographic features of RHD are unclear, if the valve lesion of the patient is mild, it would be complicated to distinguish from other forms of valvular diseases, particularly when this regards the aortic valve. Therefore, in this study, have been used strict diagnostic criteria for RHD, which might also miscalculate the true prevalence of RHD.

Our participants were comparatively old and 6 of 15 were diagnosed for the first time. This may reflect that the progress in health care resulted in these participants having their RF treated in advance which would have resulted in silent or/and less severe symptoms during the chronic phase. It has been reported that nearly half of elderly patients with RHD suffer from

different degrees of heart failure when their valve disease is identified. By physical examination, only 18% of diagnoses were made. In this survey indicated that nine of the fifteen RHD patients had cardiac murmurs and the same percentage reported to the hospital with heart failure. Thus, these results show that echocardiography is more responsive in detecting uncomplicated RHD than physical examination and clinical symptoms.

Limitation investigated only urban and suburban communities, the result may miscalculate the actual prevalence of the disease in China.

In wrapping up, the prevalence of RHD is as a minimum 10 times more in China than in developed countries, affecting roughly 2 million middle-aged to elderly Chinese (approximately estimated according to 1995 countrywide census survey data), which constitutes a considerable health burden. Health authorities and society must identify and address this inequality between the prevalence of RHD in developed and developing countries.

WHO Response

In 2018, the World Health Assembly adopted resolution WHA 71.14 calling for WHO to launch a coordinated global response to rheumatic heart disease and rheumatic fever. The Organization is working to develop clinical guidelines for rheumatic heart disease and with the help of WHO regional offices, a work plan is being developed to put interventions in place to prevent rheumatic heart disease and care for people already living with it.

Ensuring a steady, quality supply of benzathine penicillin is also a key priority in the 13th WHO General Programme of Work, specifically the strategic priority on universal health coverage; access to medicines, vaccines, and health products. Additionally, the WHO Road map for access to medicines, vaccines, and other health products 2019-2023 and the WHO Benzathine Penicillin Technical Working Group are working to address global supply and demand issues for benzathine penicillin and ensure a quality-assured, safe and effective product is available on the shelves when needed.

Mitral Valve Disease

Mitral Valve Stenosis or Mitral Stenosis

Mitral valve stenosis (MVS) or mitral stenosis (MS) is a term that is characterized by the narrowing of the mitral valve's (MV) orifice of the heart. This narrowing blocks the valve from opening appropriately, the blood flow through the heart and from the heart to the whole body get obstructed. MVS makes exhausted and short of breath, along with other problems (Carabello, 2005).

Atrial fibrillation is a common complication of resulting left atrial enlargement, which can lead to systemic thromboembolic complications like stroke (Davidson, & Stanley, 2014).

The treatment options for mitral stenosis include medical management, mitral valve replacement by surgery and percutaneous mitral valvuloplasty by a balloon catheter (Mitral Stenosis, 2021).

Natural history

The natural history of mitral stenosis secondary to rheumatic fever (the most common cause) is an asymptomatic latent phase following the initial episode of rheumatic fever. This latent period lasts an average of 16.3 ± 5.2 years. Once symptoms of mitral stenosis begin to develop, progression to severe disability takes 9.2 ± 4.3 years.

In individuals having been offered mitral valve surgery but refused, survival with medical therapy alone was 44 ± 6% at 5 years, and 32 ± 8% at 10 years after they were offered correction (Wayback Machine, 2016).

Mitral stenosis etiology and pathophysiology

Etiology: More or less all cases of mitral stenosis (MS) are due to disease in the heart secondary to RF and the resulting RHD (Agabegi & Agabegi, 2008; Mitral Stenosis, 2009). Rare causes of MS are calcification of the mitral valve leaflets, and as a type of congenital heart disease (CHD). However, there are main causes of MS that start from a cleft MV. Other causes consist of Bacterial endocarditis where the vegetation may help increase the risk of stenosis. That is the major common valvular heart disease in pregnancy (Gelson, Gatzoulis, & Johnson, 2007).

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is a valve heart disease characterized by the surrogate of an abnormally thickened mitral valve leaflet into the left atrium during systole. There are different types of MVP, largely classified as classic and nonclassic. In the nonclassic type, MVP has a little risk of complications. In severe cases of classic MVP, complications consist of MR, infective endocarditis, CHF, and in unusual conditions cardiac arrest, usually resulting in sudden death.

The identification of MVP is based on echocardiography, which uses ultrasound to visualize the MV. Early studies expected a prevalence of 38% among healthy young adults; with developed echocardiographic techniques and clear diagnostic criteria, the accurate prevalence of MVP is estimated at 2-3% of the population (Hayek, Gring, & Griffin, 2005).

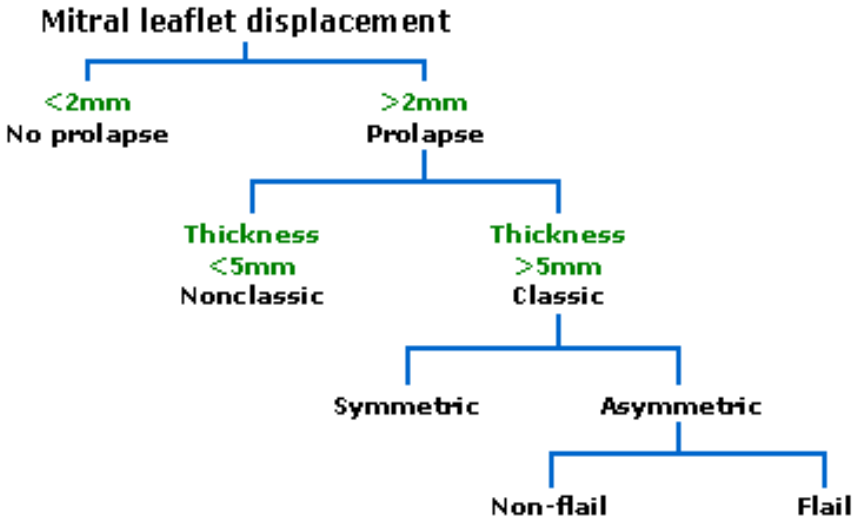

Figure 1. Diagnosis of MVP is dependent upon modern echocardiographic techniques which can identify abnormal leaflet thickening and other associated pathology

Mitral prolapse etiology and pathophysiology

Etiology: Previous to the strict criteria for the diagnosis of MVP, as explained above, the incidence of MVP in the general population varied greatly (Playford & Weyman, 2001). Some studies evaluated the incidence of MVP at 5 to 15 percent or even higher (Levy, & Savage, 1987). One study estimated MVP is up to 38% of healthy adolescents (Warth et al., 1985).

Recent clarification of mitral valve anatomy and the development of three-dimensional echocardiography has resulted in enhanced diagnostic criteria, and the true prevalence of MVP based on these criteria is expected at 2-3%. As part of the Framingham Heart Study, for example, the occurrence of MVP in Framingham, MA was estimated at 2.4%. There was a near-even split between classic and nonclassic MVP, with no considerable age or sex

discrimination (Freed et al., 1999). MVP is observationally studied in 7% of autopsies in the United States.

Pathophysiology

Classic (primary) MVP. In classic MVP, continuously advance myxomatous changes in leaflets result in MR that may get worse with the passage of time. MVP-related MR produces volume overload of the left ventricle and left atrium. Preload increases and the left ventricle dilates in order to continue a normal forward flow. However, the increase in afterload resulting from left ventricle dilatation is compensated by the fact that the ventricle is pumping much of its volume, including regurgitant volume of blood, into a low-impedance circuit, the left atrium. For that reason, afterload may be variably reduced at the start in MR and characteristically becomes elevated only in later stages of the disease as left ventricle size increases additionally. Therefore, ejection indices such as ejection fraction are not considered dependable measures of left ventricle contractile function and remain in the normal range when contractility is already deterioration (Griffin, 2006). Chordal elongation and leaflet prolapse often result in chordal rupture with immediate impairment in MR due to flail leaflet and loss of coaptation.

Non-classic (secondary or functional) MVP. Secondary or functional MVP takes place at that time when histologically normal valves prolapse. This happens due to an imbalance of geometric features that normally rule mitral valve mechanical function such as left ventricle size, mitral annular dimensions, and mitral leaflet size. For example, in younger women who are volume insufficient, a disproportionately small left ventricle cavity dimension may result in prolapse (Lax, Eicher, & Goldberg, 1992). Another example is the incidence of MVP associated with secundum atrial septal defects (Schreiber, Feigenbaum, & Weyman, 1980).

Surgical Replacement of Mitral Valve

Replacement of the mitral valve is a cardiac surgery procedure in which a patient's mitral valve is replaced by a different valve. Mitral valve replacement is performed usually robotically or manually when the valve becomes too tight and rigid (mitral valve stenosis) for blood to flow into the left ventricle, or too loose and wobbly (mitral valve regurgitation) in this case blood can escape into the left atrium and back up into the lung.

A mitral valve replacement or repair is performed to treat severe cases of MVP, heart valve stenosis, or other valvular diseases. Since a mitral valve replacement is an open heart surgical procedure, it needs placing the patient on cardiopulmonary (CPB) bypass to stop blood flow through the heart when it is opened up.

Some surgeons will first suggest repairing the valve instead of replacement, but if the patient is not a good candidate or not in a good condition to repair, then the valve must be replaced.

Many mitral valves can be repaired, particularly if the leak is due to wear and tear. When the valve is too damaged to repair, the valve should be replaced with an artificial valve. There are some advantages to repairing a mitral valve than replacing it. Some of these advantages are lower mortality during the operation (1-2% for repair versus 6-8% for replacement), an appreciably lower risk of stroke, a lower rate of endocardial infection, and enhanced long-term survival. Patients who are given a valve repair remain on the same survival curve as the normal population. Life-long maintenance on blood thinners is required after mechanical mitral valve replacement; on the other hand, after mitral valve repair, blood thinners are not required (Cleveland clinic, 2007).

Types of Valves

There are two types of artificial mitral valves, a metal or mechanical valve and a tissue valve or biological valve. The mechanical valves are made entirely from metal and pyrolytic carbon and last a lifetime. With this mechanical valve, patients are needed to take blood-

thinning medications to prevent clotting. The tissue valve is made from animal tissues. The tissue valve doesn't necessitate a patient to take blood thinners, but it only lasts 10 to 15 years. The selection of which type of valve to use should be made by the patient and his doctors taking the following into consideration: patient's age, medical condition, preferences with medication, and lifestyle.

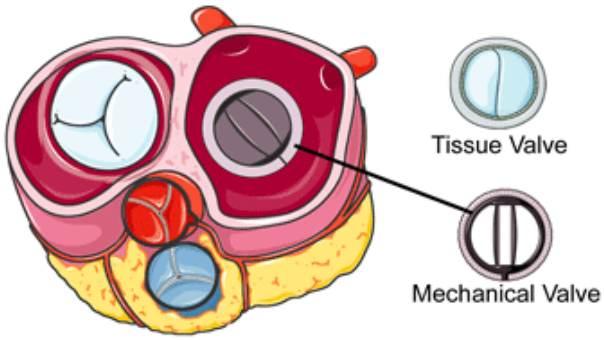

Figure 2. Mitral valve replacement with tissue or mechanical valve option

Details of the Procedure

A mitral valve replacement procedure is performed under general anesthesia, which will stay the patient asleep during the whole surgical procedure. The preferred technique is vertical sternotomy is the commonest generally recommended approach, to get to the heart. After the heart is exposed, blood must be rerouted to a heart-lung machine (cardiopulmonary bypass/CPB) (Click, Abel, & Schaff, 2000). To expose the mitral valve, an incision is made in the left atrium. The valve is then replaced with either a mechanical valve or a biological valve. Then after the functioning of the new valve is established and confirmed, the heart is then closed with sutures. The patient is then taken off the CPB and blood is allowed to flow into the coronary arteries. If the heart does not beat on its own, an electric shock is given by the electro cardioversion used to start it. Then the chest is closed up

Cardiopulmonary Bypass

Cardiopulmonary bypass (CPB) is a system that temporarily takes over the function of the heart and lungs during operation, maintaining the blood circulation and the oxygen content of the body. The CPB pump itself is referred to as a heart-lung machine or "the pump". Perfusionists are operated CPB pumps in association with surgeons who attach the pump to the patient's body. CPB is a type of extracorporeal circulation.

Surgical procedures in which cardiopulmonary bypass is used:

- Coronary artery bypass surgery;
- Repair of large septal defects (atrial septal defect, ventricular septal defect, atrioventricular septal defect);
- Transplantation (heart transplantation, lung transplantation, heart-lung transplantation);
- Pulmonary thrombectomy;
- Repair of some large aneurysms (aortic aneurysms, cerebral aneurysms);
- Cardiac valve repair and/or replacement (aortic valve, mitral valve, tricuspid valve);
- Repair and/or palliation of congenital heart defects (Tetralogy of Fallot, transposition of the great vessels);
- Pulmonary thromboendarterectomy.

Cardioplegia

Cardioplegia is temporary and on-purpose termination of cardiac activity, primarily for cardiac operation (Bosher & Westaby, 1998). Cardioplegia means cardio-the heart and plegia means paralysis. Technically it means stopping or arresting the heart so that surgical events can be completed in a bloodless and still field. Most commonly, on the other hand, the word cardioplegia refers to the solution used to bring about asystole of the heart, or heart paralysis.

The four chief goals of hypothermic cardioplegia are:

1) Immediate and continued electromechanical inactive;
2) Quick and sustained homogeneous myocardial cooling;
3) Maintenance of therapeutic additives in effective concentrations;
4) Periodic washout of metabolic inhibitors.

The most common method for accomplishing asystole is infusing cold cardioplegic solution into the coronary circulation. This method protects the myocardium, or heart muscle, from damage throughout the period of ischemia (Geissler, & Mehlhorn, 2004).

To accomplish this, the patient is first placed on CPB. This apparatus, otherwise called the heart-lung machine, takes over the function of gas exchange by the lung and blood circulation by the heart. Afterward, the heart is disconnected from the rest of the blood circulation by means of an occlusive cross-clamp located on the ascending aorta proximal to the innominate artery. Throughout this period of heart isolation, the heart is not getting any blood flow and therefore no oxygen for metabolism. As the cardioplegia solution circulates to the whole myocardium the ECG (electrocardiography) will change and eventually asystole will develop. Cardioplegia makes the metabolic rate of the heart muscle lower, by this means preventing cell death during the ischemic period of time.

Physiology

During open-heart surgery, the ischemic myocardium is protected from cell death by means of a cardioplegic solution. This protection is achieved by reducing myocardial metabolism through a reduction in cardiac workload and by the use of hypothermia.

Chemically, most of the cardioplegic solutions have high potassium concentrations in decreases the membrane resting potential of cardiac cells. The normal resting potential of ventricular myocytes is approximate -90mV (Hensley, & Martin, 1995).

When extracellular cardioplegia displaces blood surrounding myocytes, the cell depolarizes more readily, i.e. at a less negative membrane potential. The depolarization causes contraction, intracellular calcium is sequestered by the sarcoplasmic reticulum via ATP-dependent Ca++ pumps, and the cell relaxes (diastole). Though the high potassium concentration of the cardioplegia extracellular prevents repolarization. The resting potential on the ventricular myocardium is about -84mV at an extracellular K+ of 5.4 mmol/l. Raising the K+ to 16.2 mmol/l raises the resting potential to -60mV, a point at which muscle fibers are inexcitable to ordinary stimuli. When the resting potential approaches -50mV, sodium channels are inactivated resulting in a diastolic arrest of cardiac activity (Hodgkin, & Huxley, 1952). Membrane inactivation gates, or h Na+ gates, are voltage-dependent. The less negative the membrane voltage, the more h gates that tend to close. If partial depolarization is produced by a gradual process such as elevating the level of extracellular K+, then the gates have ample time to close and thereby inactivate some of the Na+ channels. When the cell is partially depolarized, many of the Na+ channels are already inactivated, and only a small part of these channels are available to conduct the inward Na+ current during phase 0 depolarization.

Fascinatingly the use of two other cations, Na+ and Ca++, also can be used to arrest the heart. The heart will not beat because the action potential is dependent upon extracellular Na ions by removing extracellular Na+ from the perfusate. Though the elimination of Na+ does

not alter the resting membrane potential of the cell. Similarly removal of extracellular Ca++ results in a reduced contractile force, and ultimate arrest in diastole. An example of a low [K+] low [Na+] solution is HTK (Histidine-tryptophan-ketoglutarate). Conversely, increasing extracellular Ca++ enhances contractile force. Increasing Ca++ to high enough level results in cardiac arrest in systole. This unluckily irreversible event is referred to as "stone-heart" or rigor.

Hypothermia

Hypothermia is the other key component of the majority of cardioplegic strategies. This is employed as a different means to further lower myocardial metabolism during periods of ischemia. The Van't Hoff equation allows calculation that oxygen consumption will drop by 50% for every 10°C reductions in temperature (Atkins, Peter, & Julio, 2006). This Q10 (temperature coefficient) effect combined with a chemical cardiac arrest can decrease myocardial oxygen consumption (MV02) by 97% (Gravlee, Davis, & Utley, 1993). And after that cold cardioplegia is given into the heart via the aortic root. Blood supply to the heart arises from the aorta root through coronary arteries is in diastole, therefore, ensuring that the heart does not utilize the valuable energy stores (ATP- adenosine triphosphate). Blood is usually added to this solution in varying amounts from 0-100%. Blood acts as a buffer and also provides nutrients to the heart during ischemia.

Once the procedure on the heart vessels (CABG- coronary artery bypass grafting) or inside the heart like valve replacement or correction of CHD etc. is over the cross-clamp is detached and the isolation of the heart is finished so that normal blood deliver to the heart is restored and the heart starts beating again.

The cold fluid (usually at 4 °C) ensures that the heart cools down to an approximate temperature of around 15–20 °C as a result slowing down the metabolism of the heart and by this means preventing damage to the heart muscle. This is more augmented by the cardioplegia component that is high in potassium.

When the solution is introduced into the aortic root (with an aortic cross-clamp on the distal aorta to limit systemic circulation), this is known as antegrade cardioplegia. While introduced into the coronary sinus it is called retrograde cardioplegia.

Ingredients

- St. Thomas' Solution
- Bretschneider Solution
- Univ of Wisconson Solution
- Custodiol HTK
- Celsior

There are several cardioplegic solutions of varying additives. The only vital additive in the majority of solutions is potassium chloride in a 20-30 mmol/L concentration range. Other additives such as mannitol, sodium bicarbonate, procaine, et cetera, are of secondary importance. Below are several generic crystalloid cardioplegia solutions.

Reperfusate

Mannitol 20% 37.5 mL
Isolyte-S pH 7.4 291.75 mL
CPD 30 mL
MSA/MSG 0.92M 70 mL
Add prior to use:
Sodium bicarbonate 62.5 mEq (62.5 mL)
Lidocaine 2% 125 mg (6.2 mL)
Nitroglycerin 1000 mcg (0.2 mL)

Ringers
Ringer's Solution 1000 mL
Potassium Chloride 20 mEq
Magnesium Chloride 32 mEq
Mannitol 20% 10 g
Sodium Bicarbonate 8.4% 6.5 mEq

Add prior to use:
Procaine 10% 2.73 mL
Maintenance
Sodium Bicarbonate 8.4% 125 mEq
Potassium Chloride 25 mEq
Mannitol 25% 15 g
Isolyte-S pH 7.4 802 mL

Cold Crystalloid Cardioplegia

Cold crystalloid cardioplegia is clinically used since the mid-1960s. It is presently applied in pediatric and adult cardiac surgery patients and remains the preferred method of myocardial protection for many cardiac surgeons.

Effective myocardial protection remains an important factor for success in heart surgery. The clinical introduction of cold crystalloid cardioplegic solutions, beginning in the mid-1960s (Bretschneider et al., 1975). May be considered an essential requirement for many of the more complex cardiac surgical procedures, which have been developed since that time. Since the 1990s, blood cardioplegia in its numerous variations has found extensive clinical application and has added considerable complexity to the field of myocardial protection. In spite of that, in many institutions around the world, cold crystalloid cardioplegia remains the preferred method of myocardial protection, due to its satisfactory clinical results, institutional experience, and individual surgeon's preference.

In principle, cold crystalloid cardioplegia protects the myocardium by hypothermia and electromechanical arrest; both of these decrease the metabolic demands of the myocardium and therefore, prolong its tolerance to ischemia. Based on the pharmacological mode of action, two types of cold crystalloid cardioplegic solutions may be discriminated: the intracellular and the extracellular solution type. Intracellular type crystalloid solutions contain no or low concentrations of sodium and calcium, while extracellular type solutions contain higher concentrations of sodium, calcium, and magnesium. Both types contain potassium between 10 and 20 mmol/l and may have added osmotically active substances such as mannitol, local anesthetics such as lidocaine and procaine, as well as buffers such as bicarbonate and amino acids. Examples for intracellular and extracellular crystalloid cardioplegias are Bretschneider's solution (CUSTODIOL®) (Ackemann, et al., 2002) and Hospital of St. Thomas solution No.2 (Plegisol®) (Chambersa et al., 1989) (respectively, Table 3).

Table 3. Composition of cardioplegic solutions

	Sodium	Potassium	Magnesium	Calcium	Bicarbonate	Other components
Custodiol® (Bretschneider's HTK solution)	15	9	4	0.015	–	Histidin, Tryptophan, Potassium-hydrogen-2-ketoglurat
Plegisol® (St. Thomas No. 2)	110	16	16	1.2	10	Lidocaine
Lactated Ringers (for comparison)	130	24	–	1.5	–	Lactate, chlorine

Note: Example for the composition of intracellular (Custodiol®) and extracellular (Plegisol®) cardioplegic solutions. All numbers in mmol/l

Cold Blood Cardioplegia

The innovative introduction of cold blood cardioplegia underscores its capacity to "prevent ischemic damage" by providing data that absolute recovery of function follows up to 4 hours of aortic clamping when cold multidose blood cardioplegia (at 20- to 30-minute intervals) is given to normal hearts (Follette et al., 1978). Unluckily, the normal myocardium is becoming a surgical rarity. The primary advantage of cold blood cardioplegia is that it couples the provision of myocardial nourishment with the capacity, during perfusion hypothermia, to lower myocardial oxygen demands and the rate and development of ischemic damage when blood supply must be interrupted to provide the technical advantages of a quiet dry operational field, or becomes maldistributed due to coronary obstruction or retrograde routes of administration (right ventricular ischemia) (Buckberg et al., 1977).

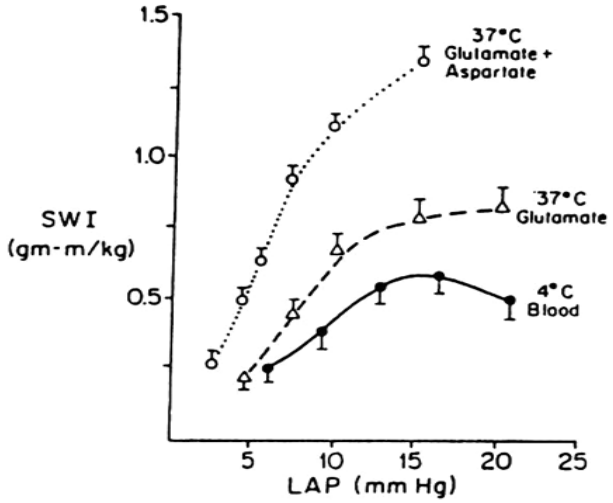

Figure 3. Left ventricular performance 30 minutes after blood reperfusion[1]

Note: (1) normal ventricular performance after warm (37°C) induction of aspartate-enriched glutamate blood cardioplegia, (2) moderate depression in ventricular performance after warm induction with glutamate blood cardioplegia, and (3) severe depression in ventricular failure after cold (4°C) blood cardioplegia; LAP = left atrial pressure; SWI = stroke work index

Material and Methods

This study was carried out in the department of cardiovascular surgery, 1st Affiliated Hospital of Xi'an Jiaotong University.

This was an observational study. The study population was the mitral valve diseased patients admitted to the department of cardiovascular surgery. A total of 20 patients were divided into two groups. Clinical data were collected from patient records, which underwent open-heart surgery for mitral valve replacement. Techniques of myocardial preservation during surgery and then clinical outcomes were compared by using cold crystalloid cardioplegia and cold blood cardioplegia in these patients. Patients were divided into two groups, Group A included 10 patients treated where cold crystalloid cardioplegia was used for myocardial preservation and Group B included 10 patients treated where cold blood cardioplegia was used in the mitral valve replacement.

Data was analyzed in both groups regarding New York Heart Association Status (NYHA), echocardiography findings, CK, CK-MB, total coronary bypass time, electrical cardioversion after declamping, and use of inotropes while coming off bypass.

[1] Reprinted with permission from Rosenkranz, E. R., Okamoto, F., Buckberg, G. D., Robertson, J. M., Vinten-Johansen, J., & Bugyi, H. I. (1986). Safety of prolonged aortic clamping with blood cardioplegia: III. Aspartate enrichment of glutamate-blood cardioplegia in energy-depleted hearts after ischemic and reperfusion injury. *Journal of Thoracic and Cardiovascular Surgery*, *91*(3), 428-435.

In the intensive care unit after the operation, duration of ventilatory support, amount of the blood drainage, use of inotropic support to keep systolic blood pressure over 100 mmHg was compared in the two groups.

All the cases underwent general anesthesia with standard median sternotomy. Routine cardiopulmonary bypass with single aortic and two-stage single venous return cannula was used. Cold crystalloid cardioplegia was used in Group A, whereas oxygenated cold blood cardioplegia was used in Group B, to arrest the heart. The oxygenated blood was delivered from the arterial line of a bypass machine on full flow O and temperature down to 30 - 28 C, cardioplegia solution used with K was added and delivered antegrade, once the aortic cross-clamp was applied. In both the techniques cardioplegia was repeated after every 30 minutes of cross clamp. The findings of the two groups were compared and statistically analyzed by t-Test and a P value less than 0.05 was considered significant.

Methods

Patient population

Only patients who had simple mitral valvular diseases and mitral valvular combined with aortic valvular diseases were included in this study protocol to exclude bias in diagnosis and operative technique. 20 patients (n=10 in cold blood cardioplegia and n=10 in cold crystalloid cardioplegia) underwent mitral valve replacement. No patients required preoperative respiratory or inotropic support.

Anesthetic protocol

All patients were premedicated with papaveratum and hyoscine; intra-arterial monitoring via the right radial artery was established under local anesthetic prior to the induction of anesthesia. Anesthesia was induced with midazolam (0.05-0.2 mg/kg), fentanyl (5-10 ug/kg). Etomidate (0.2-0.3 mg/kg) and vecuronium (0.08-0.12 mg/kg) and anaesthesia was maintained with isofluorane (0.5% to 1.5% inspired), and propofol (2-4 mg/kg.h). During CPB propofol (2-4 mg · kg–1 · h–1) was given in addition to fentanyl (2-4 ug/kg.h).

Protocol of myocardial protection

The extracorporeal circulation was performed with a Stöckert roller pump with a pulsatile flow control (PFC III; Stöckert Instrumente GmbH, Munich, Germany). The circuits were primed with 500 mL of Ringer acetate and 1000 mL of a mixture of hydroxyethyl starch 130/0.4 and sodium chloride injection. Systemic heparinization was reduced (activated clotting time [ACT] >250 seconds) in all first-time operations, and a full heparin dose (ACT >480 seconds) was administered. The standard sizes of the aortic and the 2-stage venous cannulas were 30F and 32F, respectively. Mild hypothermia (blood temperature 31°C) was instituted immediately after the start of bypass. A cardiotomy suction line was available and regularly used during CPB. After the aortic declamping, if ventricular fibrillation persisted for a few minutes, electrical defibrillation was applied to restore normal sinus rhythm.

Group A

The blood cardioplegia was mixed at the ratio of 1:4. Initially, the volume was given 500 to 800 mL Until cardiac arrest and if the return of electrical activity was seen, afterward 300 mL was given. The temperature ranged between 6°C and 10°C.

Table 4. Composition of blood cardioplegia

Na^+ (mmol/L)	97.7 ± 1.2
K^+ (mmol/L)	18.1 ± 0.3
Cl^- (mmol/L)	90.4 ± 0.8
Ca^{2+} (mmol/L)	0.73 ± 0.01
pH	7.51 ± 0.01
HCO_3^- (mmol/L)	19.2 ± 0.3

Hematocrit (%)	18.6 ± 0.6
Osmolarity (mOsm/L)	339 ± 3.1

The composition of the cardioplegic solutions is shown in the above Table 4.

Group B

The cardioplegic solution was mixed in Ringer acetate and stored at 4°C.

Table 5. Composition of crystalloid cardioplegia

Na^+ (mmol/L)	153
K^+ (mmol/L)	28.5
Cl^- (mmol/L)	159.7
Ca^{2+} (mmol/L)	2.16
pH	7.51 ± 0.01
HCO_3^- (mmol/L)	23.8 ± 0.3
Osmolarity (mOsm/L)	339 ± 3.1

Measurements of cardiac markers, echocardiography, and NYHA

As markers of myocardial damage, serum concentrations of CK, CK-MB, and Tn1 were measured at 3 points during the study protocol as follows: before a day of operation, after 30 minutes of CPB, and the next morning of the operation. All blood samples were collected through a venous and centrifuged immediately. Ef and LVD and NYHA were measured pre-operation, intra-operation, and post-operation.

Statistical analysis

Comparison of the 2 groups was done by using the T-test for continuous variables. Chi-Square Test was performed for categorical variables like ECV after declamping, use of inotropes agents when CPB stop and postoperation to keep the systolic blood pressure over 100 mmHg.

Results

Table 6. Demographic Details

Parameters	Group "A" (CBC)	Group "B" (CCC)
No. of patients	10	10
Age	37-61 years; mean 51.1 years	24-62 years; mean 45.7 years
Sex	Male 20%; Female 80%	Male 30%; Female 70%

This study comprised 20 patients. Group A (n= 10) included patients in whom cold blood cardioplegia was used for myocardial protection and group B (n=10) included patients in whom cold crystalloid cardioplegia was used. Female sex was predominant in both groups, 75% versus 25 % (Table 6). There was no difference in NYHA of patients in both groups and so was echo, Ef, LVd and LVs (Table 7).

Table 7

NYHA Functional class	Group "A" n = 10	Group "B" n = 10	P value
1	10 %	50 %	> 0.05
11	70 %	50 %	>0.05
111	20 %	0 %	>0.05
Echocardiography			

EF	> 0.05
LVd	> 0.05
LVs	> 0.05

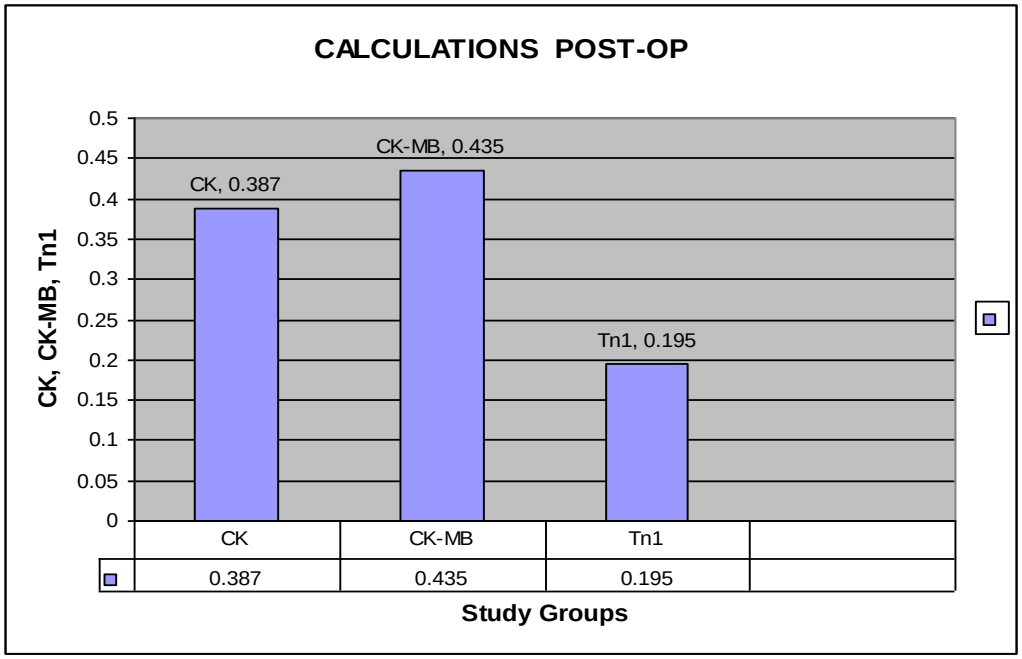

Figure 4

In this study, the cardiac markers CK, CK-MB, Tn1 were measured to evaluate the function of the heart after using two types of cardioplegia. There was no significant difference in CK between patients of group A and group B (P > 0.05) after surgery and during the operation after 30 minutes of CPB, which similarly happened in CK-MB. But there was a significant difference between the two groups in Tn1 (< 0.05) after 30 minutes of CPB.

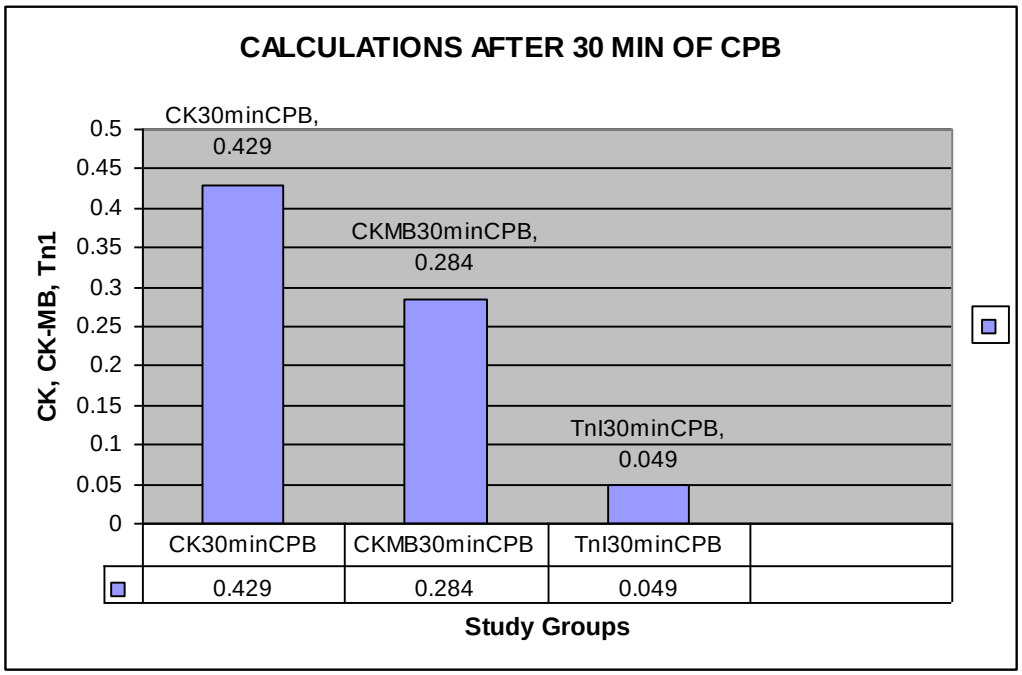

Figure 5

During operation, there was no significant difference between cardiopulmonary bypass time in two groups i.e., mean 160 minutes versus 108.8 minutes. Likewise, electrical cardioversion was needed in 10% in group A's patients and 10% also in group B's patients after declamping so there was no significant difference in both groups (Table 8). Use of inotropes while coming off the bypass in group A (90%) as compared to group B (50%), which shows a significant difference between the two groups.

Table 8. Intraoperative parameters in two groups

Parameters	Group "A"	Group "B"	P value
CPB Time	73-180 min Mean = 160 min	77-189 min Mean = 108.8 min	> 0.05
ECV after declamping	10 %	10 %	> 0.05
Use of inotropes while coming off bypass	90 %	50 %	< 0.05

There was no significant difference (P > 0.05) in ICU time, ventilator time, blood drainage, and use of inotropes to keep the BP over 100mmHg in two groups Table 9.

Table 9. Post-operative parameters in two groups

Parameters	Group "A"	Group "B"	P value
ICU time (Hrs)	21- 64 hours Mean = 34.3 hours	21-39 hours Mean = 26.6 hours	> 0.05
Duration of ventilator (Hrs)	6- 38 hours Mean = 12.2 hours	7- 20:30 hours Mean = 113 hours	> 0.05
Blood drainage	150- 7900 mL Mean = 1651 mL	570- 3280 mL Mean = 1492.5 mL	> 0.05
Use inotropes to keep BP over 100 mmHg	60 %	80 %	> 0.05

Discussion

Follette and colleagues in 1978 introduced blood as a vehicle for the delivery of cardioplegia and demonstrated that when blood cardioplegia was combined with hypothermia, it provided excellent myocardial protection during prolonged aortic cross-clamping (Follette et al., 1978). Cold crystalloid cardioplegia has been clinically used for approximately 40 years. And introduced into clinical practice in the mid-'70s. The proposed dual cardioplegia methods (Buckberg-Del Nido or Buckberg-Beyersdorf) result in a still more complex procedure that needs cell saver and hemofiltration strategies to avoid hemodilution or multiple-dose delivery (Kim et al., 2014).

The use of a cardioplegia solution to arrest the heart during surgery is cold crystalloid cardioplegia or cold blood cardioplegia is reducing myocardial damage. Now a day, a large variety of potassium-based solutions are used by the majority of surgeons. According to one of the surveys, 28% of surgeons used crystalloid and 72% use blood cardioplegia.

A large number of laboratory studies have absorbed blood versus crystalloid cardioplegia, and most of them have indicated an advantage of blood cardioplegia. But, this has not up to now been significant clinical outcome variables.

Previous studies have confirmed that microvascular endothelium and LV function are impaired after exposure to cardioplegia and cardiopulmonary bypass but in our study, there is no significant difference in left ventricular diastolic and systolic dimensions after surgery

which gives a confirmation of both cardioplegia groups have the same effect on left ventricular function (Sellke et al., 1993).

In the present study of mitral valve patients, with a mean ischaemic period, no major differences could be demonstrated for any outcome variables whether the myocardium was protected with intermittent, antegrade cold blood cardioplegia or intermittent, antegrade cold crystalloid cardioplegia.

Another study from Izmir analyzed the glucose and oxygen consumption of myocardium during arrested heart in blood cardioplegia and crystalloid cardioplegia group apart from other clinical parameters. This study also concluded that there is more oxygen and glucose consumption by the myocardium in the crystalloid cardioplegia group.

Some studies have not addressed the clear benefit of blood cardioplegia concerning clinical outcome; one group evaluated intraoperative left ventricular function and found no difference between blood cardioplegia and crystalloid cardioplegia.

A limitation of our study was the fact that the two groups were operated was a small sample size. Though, there were no differences in management or surgical technique. The decline of CK-MB was consistent for all surgeons. Considering that most had already had long experience of crystalloid cardioplegia before the area of blood cardioplegia, the impact of a learning curve on myocardial protection from 1998 to 2001 is a far possibility. It has also been concluded in our study that the use of elective cardioversion by blood cardioplegia and crystalloid cardioplegia is the same (10% vs 10%). Similarly in this study, it was found that Tn1 is raised in the cold crystalloid cardioplegia group as compared to the cold blood cardioplegia group after 30 minutes of CPB. Another study was conducted from July 1993 to Dec 2004. Clinical data were retrieved from the Department of Cardiovascular Surgery[]that the use of blood as a medium for cardioplegia results in a better outcome of these cardiac surgery patients due to well-protected cardiac tissues during aortic cross-clamping. It is essential to understand and use the various techniques to obtain the desired protective effect. Some surgeons who are not familiar with blood cardioplegia criticize it as unmanageable and too complicated compared to the simpler administration of crystalloid cardioplegia. However, in this case, simplicity and safety are not equal. Cardiac damage from insufficient myocardial protection leading to low-output syndrome can prolong hospital stay and cost and may result in delayed myocardial fibrosis.

Being passionate about blood cardioplegia, we were to some extent disappointed after realizing that no overall clinical benefits were seen when comparing blood cardioplegia and crystalloid cardioplegia. Even further, no beneficial effects could be shown in groups of patients at higher operative risk, such as those with unstable angina, lower ejection fraction, diabetes, or older age. In fact, a small number of patients with a higher preoperative risk score were available for analysis, but no statistically significant differences were demonstrated. A general limitation of the study might be the relatively short mean ischemic time and CPB time.

In summary, in this study including patients undergoing Mitral valve replacement, there were no significant differences in any major clinical endpoints whether the myocardium was protected with cold blood cardioplegia or cold crystalloid cardioplegia. The extra costs related to mechanical pumps and disposable equipment might be saved.

Conclusion

We conclude that cold blood cardioplegia is not a superior method for myocardial protection during cardiac surgery as compared to cold crystalloid cardioplegia. The use of blood as a medium for cardioplegia results in a better outcome for these cardiac surgery patients due to well-protected cardiac tissues during CPB. Cold crystalloid cardioplegia provides better myocardial metabolic status resulting in less chance of low use of inotropic agents postoperatively.

There is no difference in cardiac function, CK, CK-MB, and troponin in both Groups. To our surprise, there was absolutely no tendency towards an improved outcome in the patients receiving blood cardioplegia, which could be expected from experimental studies. However, the definite answer considering the best technique for myocardial preservation achieves to need a large prospective multicentre study, including thousands of patients. There is increased TnI during surgery after 30 minutes of CPB in the group of cold crystalloid cardioplegia, TnI has a high sensitivity than CK, CK-MB and we concluded that cold blood cardioplegia maybe decreases the myocardial damage. There is no better effect of cold blood cardioplegia may be the reason is the long time of CPB than the cold crystalloid cardioplegia.

Comparing blood and crystalloid cardioplegia, we are unable for reaching statistical differences with sufficient power because of small sample sizes. In our study, we observe a significantly lower incidence of low output syndrome (LOS) and TnI release with cold crystalloid cardioplegia and use of inotropic agents more in cold blood cardioplegia. On the other hand, these conclusions are debatable, as our sample size was small and absent of basic characteristic measurements. A limitation of the study may be that the sickest patients (severe cardiac or renal failure, aortic valve, etc.) were included, which might have given different results. However, for the patient population under investigation, the conclusions may be regarded even strengthened by the standardized patient management, and the consistent application of the same procedures over time. Enrolment of a larger number of patients, or even more high-risk patients, would have been ideal, but clinical studies are continuously challenged by changes in clinical practice over time, which again challenge the strength of the results.

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