REVIEW ARTICLE

Rev Bras Cir Cardiovasc 2008; 23(1): 97-107

Myocardial protection to the hypertrophied heart: the eternal challenge

Proteção miocárdica ao coração hipertrofiado: o eterno desafio

Elthon Silveira CRESSONI[1], Luiz Ernesto AVANCI[2], Domingo Marcolino BRAILE[3], Antonio Carlos CICOGNA[4], Ana Paula Marques LIMA-OLIVEIRA[5], Milena Alonso Egéa GEREZ[6], Antonio Sérgio MARTINS[7]

RBCCV 44205-955

Abstract

The myocardial protection allowed great advance in cardiac surgery, decreasing the mortality and making more feasible complex surgeries. Latterly the patient population elected for cardiac procedures has been changing towards elderly patients with ventricular function depressed and myocardial hypertrophy. The myocardial hypertrophy condition represents a great challenge since the beginning of the cardiac surgery. Several techniques have been described to protect the myocardial hypertrophy, however with no satisfactory results. In this manuscript we present the state of the art technique of myocardial protection.

Descriptors: **Cardioplegic solutions. Hypertrophy, left ventricular. Hypertrophy, right ventricular. Heart arrest, induced/methods.**

1. Master Degree (Unesp Botucatu - Faculdade de Medicina), Braile Biomédica Cardiac Researcher Independent Veterinarian.
2. M. D.
3. Unicamp and Famerp Professor Livre Docente, Editor of BJCVS. Director of FAMERP Post-Graduation Program.
4. Full Professor of Cardiology, Faculdade Medicina de Botucatu.
5. Doctorage Degree, Biologist.
6. Graduated in Medicine at the Universidade de Marília.
7. M. D., Professor of Faculdade Medicina de Botucatu.

This study was carried out at Faculdade de Medicina de Botucatu, Botucatu, SP, Brazil.

Correspondence address:
Elthon Cressoni. Av. Juscelino Kubitschek de Oliveira, 1505 - São José do Rio Preto – SP – Brasil - CEP 15091-450.
E-mail: kardiovet@kardiovet.com.br

Received: August 31, 2007
Approved: February 8, 2008

Resumo

A proteção miocárdica permitiu enorme avanço na moderna cirurgia cardíaca, reduzindo a mortalidade e permitindo que operações cada vez mais complexas pudessem ser realizadas. A alteração na população eleita para procedimentos cirúrgicos cardiológicos mudou significativamente nas últimas décadas, com o aumento de pacientes mais idosos, com função ventricular deprimida e miocárdio hipertrofiado. Essa última condição, desde os primórdios da cirurgia cardíaca, constituiu-se em grande desafio. Diversas técnicas de proteção ao miocárdio hipertrofiado foram descritas, porém com resultados não alentadores. As características da hipertrofia miocárdica no adulto com cardiopatia cirúrgica apresentam particularidades desafiadoras. Nesse artigo, procuramos atualizar o estado da arte sobre a proteção miocárdica ao coração hipertrofiado.

Descritores: **Soluções cardioplégicas. Hipertrofia ventricular esquerda. Hipertrofia ventricular direita. Parada cardíaca induzida, métodos.**

INTRODUCTION

From the beginning, the cardiac surgery have received great contributions from scientific and technological advancements [1], especially after the dramatic breakthrough generated with the introduction of the cardiopulmonary bypass (CPB), in 1953, by Gibbon. Currently, the worldwide groundbreaking development of ortheses, prostheses, devices, and drugs has allowed a greater amount of patients to get benefits from cardiac surgery.

Nevertheless, the adequate protection of the hypertrophied myocardium during surgical procedure is still an eternal challenge, because it is known that this heart already presents ultrastructural changes due to a higher work overload with low blood requirement, once during the cardiac surgery procedure is desirable to have as less blood as possible in the surgical field and the heart should be standstill and flaccid to be better visualized and to allow the surgical technique to be carried out. However, the technology available to maintain the heart adynamic through an adequate period involves the reduction of blood perfusion. Yet, it is of common knowledge that the myocardium does not support long periods of time in such a condition because the cardiac metabolism is sufficiently high to maintain cellular integrity and mechanical activity [2].

In this way, throughout cardiac surgery history, the increasing need of myocardial protection follows its evolution, imposing challenges to all those who dedicate themselves to the specialty in developing techniques and drugs that increase the myocardium tolerance to ischemic periods, including pharmacologists, physiologists, pathologists, perfusionists, anesthesiologists, and surgeons [2], thus contributing to better preserve myocardial function [3], i.e., to allow interrupting its electromechanical activity without producing either structural or functional injury aiming at to facilitate the repair of existing cardiac lesions.

Among the myocardial protection techniques, we have aortic clamping [4], hypothermia with ventricular fibrillation [5], hypothermic crystalloid cardioplegia [6], oxygenated hypothermic crystalloid cardioplegia [7], intermittent cold blood cardioplegia [8], intermittent warm blood cardioplegia [9], cold or warm continuous blood cardioplegia [10], continuous tepid blood cardioplegia [11], and whole blood cardioplegia (minicardioplegia) [12].

A great myocardial oxygen consumption variation occurs during cardiac surgery, which is lowest over the cardiac standstill induced by cardioplegic solutions and greatest at the cardiopulmonary bypass exit. Thus, without an adequate myocardial protection, postoperative morbid-mortality and the risk of developing ischemic contracture of the left ventricle, also known as stone heart, or late myocardial fibrosis are increased. Robinson et al. [13], in 1995, examined the method of myocardial protection used by North-American surgeons in the United States and they found that 98% of the cardiovascular surgeons used cardioplegic standstill and that 60% of them used blood cardioplegia, 22% crystalloid cardiolegia, and 6% oxygenated crystalloid cardioplegia. Regarding the cardioplegic solution delivery pathway, 36% used the antegrade pathway, 4% the retrograde pathway, and 60% both pathways. Only 10% of the patients used continuous warm cardioplegia. Despite the lack of official statistics, intermittent clamping and crystalloid cardioplegic solutions are in full vogue in Brazil.

MYOCARDIAL HYPERTROPHY

Myocardial hypertrophy is considered as the most efficient event among the compensatory mechanisms of heart diseases when the muscle is exposed to the work overload depending on extramyocardial disease [14].

Several mechanical and neurohormonal factors act as myocardial growth factors and change the pattern of protein synthesis, resulting in a ventricular remodeling. The several mechanisms in response to the decrease of cardiac performance, initially adaptive, became developmentally pernicious [15].

The cardiovascular system is the first of the major systems to function in the embryo. During the intra-uterine life it is known that the growth and development of the heart happens mainly from cell hyperplasia. After birth, the ventricle walls are affected by the difference of

pressure overload between both ventricles, thus occurring left ventricle hypertrophy (submitted to the highest pressure overloads) and hypertrophy of 20% of right ventricle (submitted to the lowest pressure overloads). The transition process is completed around the fourth or fifth weeks after delivery [16]. So, the proliferative capacity is maintained for a definite period of time in life after birth, so that cell hypertrophy is the mechanism that gives continuity to increase of cardiac mass until its complete development into adult life. The physiologic growth of the heart occurs in such a harmonic way among its constituents without impairment to the functional characteristics of cardiac muscle [17].

The hypertrophy of the myocardium which is under hemodynamic stress differs from the physiologic hypertrophy which occurs during its development and does not correspond to just the increase of normal myocardial mass [18] due to its low capacity of cell division [19]. From the histological standpoint, the alteration of the myocardial architecture involves hypertrophy and loss of myocytes, fibroblasts hyperplasia, and collagen deposition [20].

The process of ventricular remodeling is influenced by several factors, such as mechanicals (volumetric or pressure hemodynamic overload) [21], neurohormonals (sympatethic, renin-angiotensin, aldosterone, and endothelin systems), cytokines, oxidative stress, ischemia or the gene expression factors which will lead to cardiomyopathies [22].

Among the mechanisms involved in this process, the major one is the hypertrophy of the myocyte. The deformation of the membrane and the changes in the cytoskeleton are detected by the myocardium that stimulates the expression of myocardial genes and the changes in the functioning of the ion channels of the sarcolema and eventually the activation of hypertrophy mediators such as the calcium-calmodulin system and calcineurina. It also stimulates the regulation of peptide growth factor production. There is also a series of neurohormones and paracrine/autocrine hypertrophy mediators, including noradrenalin, angiotensin II, endothelin 1, Fibroblast Growth Factor (FGF), TGFβ 1, proinflammatory cytokines (e.g., TNF-α), and G proteins. By means of signal transduction proteins (Ras, Gaq, Gas) these mediators transmit their signs, activating enzymes (protein kinase C [C-PKC], mitogen-activated protein kinase [MAPK]) which induce the fetal gene expression, constituting the hallmark of pathologic hypertrophy which includes gene alterations involved in the synthesis of contractile proteins, management of intracellular calcium, natriuretic peptides, among others. Concurrently with these changes, there is still fibroblast proliferation and changes in the synthesis of extracelullar matrix which participate in the genesis of remodeling [23] (Table 1).

Table 1. Changes found in cardiac remodeling. Adapted from Cicogna et al. (2000).

Myocytes	Hypertrophy
	Necrosis
	Apoptosis
Contractile proteins	Isoform
	Myosin heavy chain
	Fetal form of the myosin
Calcium transit	light chains
	Calcium channel alterations
	Calmodulin
	SR-Ca^{++}-ATPase
Beta-adrenergic route	Fosfolambam
	Beta1-receptors
	Gs protein
	Gi protein
Energy	Adenyl cyclase activity
Extracellular matrix	ATP
	Metalloproteases
Cytoskeleton	Fibroses
	Tubulin
	Desmina disorganization
	Titin

Myocardium presents 70% of myocytes [24] and the remaining consists of a number of other cell types, vessels, and interstitial collagen matrix. The balance among these three compartments contributes to maintain heart shape and function [25]. Changes in the composition of these compartments, especially in the collagen – a substance having relatively high tensile strength to stretching – when in abnormal quantities in the myocardium, result in increased passive muscle stiffness and left ventricle diastolic dysfunction. This phenomenon is mainly observed when pressure overload is present [25,26]. Current studies have suggested that muscle stretching imposed by volume overload favors collagen degradation in a process that might involves mastocyte degranulation. They also suggest that volume or pressure overloads cause distinctive patterns of heart remodeling [26].

MYOCARDIAL PROTECTION

Under normal conditions, cardiac metabolism is essentially aerobic with great amount of energy synthesis and consumption. Fat acids are degraded and their metabolites take part in the following processes: oxidative phosphorylation, Krebs cycle, and respiratory chain. Fat acids constitute the main energy supply to the myocardium.

Nevertheless, glucose plays an important role in this metabolism, once several constituents of their degradation are critical to Krebs cycle adequate functioning [27].

During ischemia, a decline of myocardial metabolism occurs, which eliminates the energy expenditure for contractile activity and focus on maintaining cellular integrity, delaying muscle contraction and relaxation through two mechanisms: initially, an increase on hydrogen ions competing for calcium ions based on troponin activation sites occurs, lentifying the actin-myosin activation and, consequently, the contraction. Afterwards, a decrease in high-energy phosphate concentrations occurs; they are important in process of calcium re-uptake into sarcoplasmic reticulum, thus jeopardizing the relaxation. In addition to these mechanisms, severe ischemia induces to anaerobic metabolism due to the absence of substrate and oxygen, occurring lactate deposition and consequent intracellular acidosis. In this way, the main determinants of post-ischemia ventricular function recovery are the duration and severity of ischemia, in addition to post-ischemia reperfusion, which may be present or not, leading to ischemic contracture of the left ventricle (stone heart) [28]. Based on this knowledge and on the description by Heyndrickx et al., in 1975, it is observed that the myocardial depression after ischemia/reperfusion is generated by two factors: through oxygen-derived free radicals binding released at the moment of reperfusion and through increased calcium intracellular concentration (*calcium overload*), which occurs during both ischemia and reperfusion, leading to severe systolic and diastolic dysfunction which can last minutes or days after cardiac surgery, bringing up the need to protect the myocardium during cardioplegia [3].

Currently, "cardioplegia" is defined as the myocardial protection during a controlled paralysis of the heart, which represents a mistake, once the exegesis of the term cardioplegia means "lesion, blow, attack, or wound", thus it is correct to use cardioplegic solution. Therefore, myocardial protection can be achieved through the aid of cardioplegic solutions added to substrates or elements allowing the desirable protection [29]. The variety of strategies which have been widely studied makes this issue a controversial one.

Myocardial protection defines the set of strategies targeting to reduce the myocardial ischemia-reperfusion lesion intensity during cardiac surgery and its consequences over myocardial function [30] because the damages to the heart due to an inadequate myocardial protection, which lead to a low output syndrome, can prolong the length of hospital stay, resulting in late myocardial fibrosis [31].

Braile et al. [32], in 1989, emphasized that the cardioplegic solution should safely promote cardioplegia, create favorable conditions to a continuous energy production, and eliminate the deleterious effects of ischemia and reperfusion. Thus, the composition of a solution should consist of elements which provide the following: 1. an immediate paralysis of the heart, avoiding energy depletion; 2. myocardial cooling, reducing metabolic requirement, or when the myocardium is kept warm, to provide sufficient flow to maintain aerobic metabolism; 3. substrates for aerobic or anaerobic metabolism, or both; 4. a buffering effect against acidosis, avoiding metabolism; 5. stabilization of the membrane using specific drugs, and 6. avoidance of edema through hyperosmolarity. All the abovementioned myocardial protection methods seek to preserve cardiac function during procedure over the heart with or without aortic cross-clamping. According to the method or myocardial conditions, lesions do occur below limit detection that cannot be perceived or yet reversible lesions after reperfusion or even caused by reperfusion itself, leading to permanent myocardial damage. These lesions should be considered as special to the hearts that have great energy deficits, as well as to the ischemic, hypertrophic, dilated, cyanotic, and immature ones. Each one of them has their own characteristics and they can or cannot resist to a greater or lower period of ischemia with different methods of hypothermic or normothermic cardioplegia, or not, with the addition of amino acids, etc [32] (Figure 1).

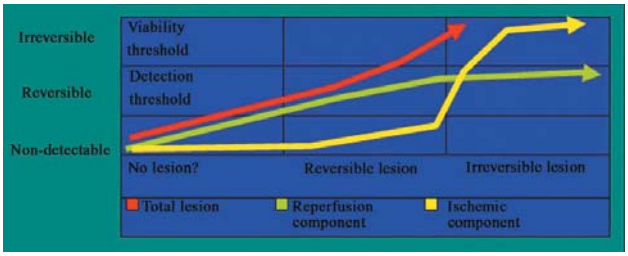

Fig. 1 – Myocardial evolutionary impairment resulting from ischemia reperfusion or complete occlusion

In brief, we can describe six main techniques types aiming at myocardial protection; however in current medical practice, several cardiovascular surgical centers adopt one type of technique and/or use a combination of different types.

Thus, we have: 1. intermittent aortic cross-clamping technique in which occurs, at least over 20 minutes, the interruption of blood flow in coronary arteries, interposing periods of reperfusion, taking into consideration that in this time interval the changes taking place into myocardial

cells are reversible and that relatively low periods of ischemia induce an effect over myocardial cells making them capable of being more tolerant to a second period of ischemia.

In this way, the cardioprotective effect of the technique is based on ischemic "preconditioning". 2. In the technique of hypothermia with ventricular fibrillation, aortic cross-clamping induces to fibrillation and myocardial protection is dependent of metabolic activity reduction caused by a fall in temperature. 3. A hypothermic crystalloid cardioplegia consists of infusing a solution with electrolytic properties slightly hyperosmolar, producing an electromechanical stopping of the heart. This solution contains substances aiming at to reduce the high-energy phosphate consumption associated with hypothermia followed by a decrease in metabolic cell activity. 4. Oxygenated hypothermic crystalloid cardioplegia follows the same principles of the previous described technique plus oxygen delivery to supply possible existing metabolic activity. 5. Hypothermic blood cardioplegia also is based on the use of hypothermia as a protective factor, but perfusion consists of blood which presents more physiologic characteristics to supply a possible cellular activity and the recovery of energetic phosphate cellular levels which can be amino acid-fortified (aspartate and glutamate). 6. Continuous tepid or normothermic cardioplegia is based on providing nutrients, metabolites, and either amino acid-fortified oxygen or not continuously aiming at to maintain cellular metabolic activity, or in certain situations to promote resuscitation of a myocardium which has undergone previous injury [2].

Regarding the composition of cardioplegic solution being either crystalloid or bloody, it is necessary the presence of an agent which will cause the paralysis of electromechanical activity of the heart, such as the following: potassium, magnesium, procaine, chelating agents, and calcium channel blockers used alone or in combination. It is important to highlight that potassium should not exceed 40-mEq/L-level in order to avoid calcium inflow into the cell and, consequently, oncosis [33].

Among the mechanism of induced cardiac paralysis by means of cardioplegic solution (hyperpolarization, depolarization or calcium pump blockers), depolarizing cardioplegia is the most current used method, but articles available in the literature already report about the possibility of using hyperpolarizing solutions that cause more marked reduction of energetic expenditure [34].

Substrates and oxygen must be added in order to assure the production of some aerobic metabolism that might be present during aortic cross-clamping. However, fortified amino acids, which are mediators of Krebs cycle, can also be added as quoted before, as well as the own supply of adenosine triphosphate (ATP) and/or creatine phosphate (phosphocreatine) [CP] can significantly improve myocardial protection [35].

Recent studies have shown the close relation of increased blood lactate levels with severity of tissue oxygen deficit and decreased oxygen delivery. The occurrence of such a condition is associated to patients' high morbidity and mortality postoperatively. For this reason, it is necessary, whenever possible, to avoid the appearance of acidosis or to treat it aggressively [36] using buffering systems which have the purpose of keeping aerobic metabolism, functioning of calcium and sodium pumps, membrane integrity and to buffer acidosis occurring during myocardial ischemia time. Several types of buffers can be used, such as sodium bicarbonate [37], phosphate buffer, imidazole, among others; however, blood is the one presenting most advantages [38].

Lidocaine is an antiarrhythmic class I-B drug capable of acting directly into transmembrane conductance of cations, mainly of sodium, potassium, and calcium. Lidocaine in association with normothermic hyperkalemic blood cardioplegia solution provides additional protective effect to ischemic myocardium during cardiopulmonary bypass [39]. Also, it can be used to stabilize the cellular membrane, besides presenting antiarrhythmic features preventing the appearance of ventricular fibrillation after myocardial reperfusion [40].

In blood cardioplegia, hiperosmolar solutions help in the prevention of edemas causing changes into cellular membrane, as well as the use of calcium chelating [41] which causes lower cellular edema with the use of minicardioplegia technique [42].

An adequate composition of a cardioplegic solution should consist also of free radical scavengers. Ischemic myocardium produces metabolites that when in contact with oxygen in the reperfusion phase will give raise to free radicals which have a definite role in tissue lesion and might be represented by radical with nitrogen or carbon nucleus, but mainly by those oxygen-derived that are the superoxide, hydroxyl ion, and atomic oxygen. The maintenance of normoxemia (PO_2 80-100 mmHg) rather than hyperoxemia during the beggining of cardiopulmonary bypass significantly reduced the oxidative lesion and myocardial dysfunction extension [43].

The studies carried out by McSord & Fridovisch [44] confirmed the capacity of the superoxide dismutase enzyme to transform superoxide into a substance less noxious to the cells, the hydrogen peroxide, which can be removed by the action of two other enzymes resulting in water as end product. From this knowledge on, ways were opened to scavengers' usage. A temporary interruption of ATP-dependent calcium (Ca++) pumps leads to increased intracellular calcium concentrations that during ischemia,

activates the xanthine oxidase administration route. Increased intramuscular calcium concentrations during aortic cross-clamping periods activate the calcium-dependent proteases that convert xanthine dehydrogenases into xanthine oxidase. Xanthine oxidase uses molecular oxygen rather than NAD+ as electron receptor, thus producing superoxide radical [45].

By understanding the mechanism of free radical formation during myocardial ischemia, we have two mechanisms to remove free radicals: 1. Using allopurinol to reduce the amount of xanthine oxidase, thus preventing the production of free radicals; or 2. Using components that act to remove formed free radicals, such as superoxide dismutase, catalase, peroxidase, manitol, vitamin E, nicotinic acid, deferoxamine, and others. With continuous normothermic perfusion, we can avoid ischemia and all natural scavengers are provided [46], even though the complete depletion mechanism of free radicals remains unclear. A study by Luo [47] using aminophylline (theophylline), a xanthine derivative phosphodiesterase inhibitor with anti-inflammatory effects suggests that intracorporeal administration reduces the release of cardiac Troponin I (cTnI) and activation of neutrophils, improving cardiac function in patients undergoing cardiopulmonary bypass for coronary artery bypass grafting.

Regarding temperature (hypothermic, normothermic, or tepid), it is worth remembering that in 1979, Buckberg [48] described the controversy about using hypothermia as a form to protect the myocardium, promoting the reduction of energy consumption by the tissue, whereas at the same time occurs a fall in its own production, hampering the functioning of ATPase-dependent calcium pump, promoting calcium ion accumulation intracellularly, while the use of tepid or normothermic cardioplegic solutions (30ºC), once the adequate substrate for maintenance of cellular metabolism is provided, reduce the risk of calcium deposition.

Yet, it must be remembered that oxygen consumption in a hypothermic myocardium is higher when artificially stimulated and that the use of hypothermia also requires hemodilution to overlap severe rheologic problems of stacks (rouleaux) of red blood cells and capillary obstruction, which are overcome through normothermia [48].

Lima-Oliveira et al. [49] through experiments showed a better preservation of myocardial cells, fibroblasts, and endothelial cells when submitted to a cardiac arrest protected by low-volume blood cardioplegic solution. Cressoni et al. [50] showed, experimentally as well, the superiority of cardiac protection by tepid, continuous cardioplegic solution in the preservation of myocardial ultrastructural and structural integrity when compared to intermittent cold crystalloid cardioplegic solution. Martins et al. [51] in a similar experiment proved the efficacy of myocardial protection fostered by retrograde, antegrade, and continuous blood cardioplegia, which allowed to further improve the outcomes, mainly those related to cardiac rhythm.

In a prospective study by Sobrosa et al. [52] involving 15 consecutive patients undergoing cardiac surgery through continuous retrograde hypothermic blood cardiolegia with normothermic antegrade induction, they came to a conclusion that this technique requires less time to attain asystolia and the improvement of myocardial protection, but it did not avoid the anaerobic metabolism during aortic cross-clamping period.

Bothe [53] reported that the myocardial protection degree provided by the administration of a retrograde cardioplegic solution varies according to the organ anatomy and that it is a safe e effective method when associated to an antegrade cardioplegic solution.

CRYSTALLOID CARDIOPLEGIA

Potassium chloride is used by crystalloid cardioplegic solutions as agent to promote cardiac arrest [54].

Several basic cellular processes need potassium participation. Among theses important functions, the maintenance of intracellular pH, excitability, contractility of muscle cells, and transmembrane potential, especially of cardiac cells, are to be highlighted. The distribution of this cation is predominantly cellular and the muscle cells are the ones that contribute to a greater storage. Potassium internal balance represents its motion between intra- and extracellular spaces; among the factors that take part in this balance are hormones (insulin, catecholamines, and aldosterone), acid-base balance, and plasmatic tonicity; the transmembrane carrier is the ATPase-dependent Na+/K+ pump [55]. It remains unknown the accurate potassium concentration required by a cardioplegic solution; currently, the solutions used vary from 16 to 25 mEq/L [56].

Magnesium, the second intracellular cation also presents cardioprotective properties by removing calcium from the mitochondrium and driving it into sarcoplasmic reticulum, besides competing with this same ion when it binds to troponin C and blocks ATP-converting enzyme action, which reduces myocardial contractility increasing cardiac reserve. Also it prevents ventricular fibrillation when administered before aortic cross-clamping [56]. High magnesium concentrations extracellularly produce cardioplegia by blocking the calcium channels into the cells.

After prolonged ischemia, when small amounts of calcium are added to cardioplegic solutions, it seems to produce a better stability of the cellular membrane, occurring less injury during reperfusion when calcium concentration is not in its subnormal level [57].

Ringer lactate solution, serum, and other solution with low sodium concentration are used as common transports of cardioplegic solutions, being the most popular solution, the St. Thomas' solution II (Table 1), developed by Hearse and Bainbridge, in England [57].

Regarding the temperature of cardioplegic solution administration, several studies from different centers have reported their experience with the use of both normothermic and hypothermic solutions. Usually, the temperature of the solutions attained by checking the interventricular septum varies from 4º to 7ºC; it is aimed a temperature between 12º and 18ºC, being that the temperature reduction depends on both the administered volume and velocity of the infusion [58].

Crystalloid cardioplegia is usually administrated by antegrade route through an inflatable pressure bag connected to a needle or a special catheter inserted into the aortic root, producing a maximum arterial pressure between 50 and 60 mmHg [59].

The method is more indicated for short-term procedures in which the ischemia time é lower than 20 minutes. The main inconveniences of this method are difficulty in monitoring the amount of administered volume and the need of having a solution filtered before filling the plastic bag [59].

BLOOD CARDIOPLEGIA

It was shown that the myocardium, even after an induced cardiac arrest and hypothermia, presents cellular activity. The use of blood cardioplegia was then started. It uses the blood perfusate as a transporter of cardioplegic solution with the main purpose of delivering oxygen and substrates and decreasing cellular damage. Blood perfusate is the most adequate transporter to infusion of cardioplegic agents, presenting important characteristics to better supply myocardium and other tissues requirements such as: 1. the presence of a natural buffer system for maintenance of and ideal pH; 2. the adequate colloidomsmotic pressure, decreasing the risk for edema of the myocytes; 3. the presence of adequate concentrations for maintenance of cellular function; 4. the capacity of giving oxygen and withdrawal carbon dioxide; 5. To supply nutrient substrates to the cells; 6. the presence of free radical natural scavengers; and 7. Do not produce severe rheologic changes.

The indicators of the superiority of blood cardioplegia over the crystalloid cardioplegia can be shown under certain circumstances, such as the performance of a surgery in the presence of myocardial hypertrophy; a surgery that requires a more prolonged cardioplegia time; pediatric cardiovascular surgery, severe ventricular dysfunction; and recent history of ischemia.

Regarding the procedure using aortic cross-clamping with duration inferior to 30-40 minutes, both blood and crystalloid cardioplegia solutions are equivalent, especially if crystalloid cardioplegia is oxygenated [60].

The addition of several components in some compositions to perfusate is what characterizes the blood cardioplegia, such as electrolytes, sodium bicarbonate, calcium chelating, vasodilators, and even insulin [61]. Furthermore, a mixture in the following proportion, four parts of perfusate and one part of crystalloid solution, which is called "mother" solution, can be presented in two forms: one is more concentrated to induce electromechanical arrest of the heart, and another less concentrated for maintenance of myocardial reperfusion and cardioplegia (Tables 2 to 5) [62].

In this kind of procedure, cardioplegia can be administered by an antegrade route, going through coronary circulation following the normal blood flow direction, applying a solution directly into the aortic root, or, selectively in both ostia of the coronary arteries, or, occasionally, into the coronary grafts. Also, it can be retrogradely delivered through the coronary sinus ostium in the right atrium, and it can go through coronary circulation into the opposite direction, being harvested in the aortic root [63].

Table 2. St. Thomas solution for crystalloid cardioplegia.

Salts	Concentrations
Sodium	6.0 mEq
Potassium	20.0 mEq
Magnesium	32.0 mEq
Calcium	4.4 mEq
Procaine	2.0 mEq
q.s.p (quantitat suficient per) excipients	40 mL

Table 3. "Mother" solution for blood cardioplegia induction.

Salts	Concentrations
Potassium chloride	75 mEq
Magnesium chloride	40 mEq
Monosodium glutamate	30 mM
Monosodium aspartate	30 mM
q.s.p (quantitat suficient per) excipients	50 ml

Table 4. "Mother" Solution for blood cardioplegia induction. The added components and the result in the modified blood, the volumes of the components into the mother solution, and the solution final concentration ready to be used are described. ACD is added to reduce blood calcium concentration; insuolin promotes the entrance of glucose into the cells; papaverine is the vasodilator agent. Adapted from Braile et al. (1991).

ADDED	MODIFIED BLOOD	VOLUME (mL)	Final concentration diluted with blood 1:4
D5W	Osm Substrate	390	340 - 360 mOsm
ACD	< Ca^{++}	30	0.5 - 0.6 mM/l
Potassium chloride	K^{+}	20	22 - 24 mEq/l
Sodium bicarbonate	pH	8	7.5 - 7.6 mEq/l
Magnesium sulfate	Mg^{++}	10	4.4 - 5.2
Simple insulin	Substrate	10 IU	2.0 IU/l
Papverine	Ca^{++}	40 mg	8 mg/l
Sodium glutamate	Substrate	40	12 mmol/l
Sodium aspartate	Substrate	40	12 mmol/l

Table 5 – "Mother" solution for blood cardioplegia maintenance/reperfusion.

Salts	Concentrations
Potassium chloride	25 mEq
Magnesium chloride	15 mEq
Monosodium glutamate	15 mM
Monosodium aspartate	15 mM
q.s.p (quantitat suficient per) excipients	50 mL

Regarding to temperature, blood cardioplegia can be delivered either hypothermically, normothermically, or tepidly [64].

Hypothermic cardioplegia is not recommended in cases of ventricular hypertrophy, severe heart failure, significant myocardial ischemia, and cardiogenic shock, among others. This technique reduces the expenditure of high-energy phosphates as well as its production during aortic cross-clamping period. However, in the abovementioned circumstances, the myocardium can already present an important metabolic deficit with a lower production of such phosphates [65].

The continuous tepid blood cardioplegia, described by Braile, aims at myocardial protection by delivering the cardioplegic solution by both intermittent antegrade and continuous retrograde routes. This kind of cardioplegia has shown to reduce ischemic and functional damage either reducing the increase of serum troponins [66,67] or as a lower increase of lactate [68] and better functional preservation [69].

The use of such antegrade/retrograde technique, repeated over each 15 minutes, allowed to further improve the outcomes, especially regarding cardiac rhythm, once the heart takes over sinusal rhythm with an adequate frequency just after the aortic cross-clamping interruption. The explanation is better understood through a better cardioplegic solution distribution, especially for regions of interventricular septum, right atrium and ventricle, including the conducting system of heart [70,71].

CONCLUSION

The concern with myocardial protection will always be one of the most important points, from the moment to decide to submit the patient to cardiac surgery on, always keeping in mind that such procedure aims at improving the patient's quality of life, especially of those who already have some degree of deficiency from cardiac muscle work.

Recent studies could have evidenced a cellular cardiac metabolic activity during the induced cardiac arrest with cardioplegic solution, thus proving the need to adequately supply nutrients and oxygen.

Yet supplying adequately substrates, there is a production of free radicals, changes in transmembrane potentials, and possibility of cellular edema, being necessary to add to the cardioplegic solution not only nutrients but also free radical scavengers and membrane stabilizers , some of them with antiarrhythmic properties.

The studies have also shown the superiority of blood cardioplegia over the crystalloid cardioplegia, especially by its more physiologic characteristics.

Regarding the temperature, the route of cardiac arrest and delivery of cardioplegic solution is still at the surgeon discretion, including his/her practice and expertise, always seeking for the best.

And, at last, regarding myocardial protection to a hypertrophied heart, experimental studies have shown the superiority of tepid blood cardioplegia in relation to hypothermic crystalloid, but this pathological entity, increasingly supervening in the population, constitutes an eternal challenge for cardiac surgeons, besides the intrinsically patient's characteristics. However, we should always have in mind that the state-of-the-art was not achieved yet.

REFERENCES

1. Buffolo E. História da cirurgia cardíaca brasileira. Disponível em: http://publicacoes.cardiol.br/caminhos/019/default.asp

2. Souza MHL, Elias DO. Fundamentos da circulação extracorpórea. 2ª ed. Rio de Janeiro:Centro Editorial Alfa Rio;2006.

3. Malbouisson LMS, Santos LM, Auler Jr JOC, Carmona MJC. Proteção miocárdica em cirurgia cardíaca. Rev Bras Anestesiol. 2005;55(5):558-74.

4. Burdette WJ, Ashford TP. Structural changes in the human myocardium following hypoxia. J Thorac Cardiovasc Surg. 1965;50:210-20.

5. Bodenhamer RM, DeBoer LW, Geffin GA, O'Keefe DD, Fallon JT, Aretz TH, et al. Enhanced myocardial protection during ischemic arrest. Oxygenation of a crystalloid cardioplegic solution. J Thorac Cardiovasc Surg. 1983;85(5):769-80.

6. Jatene AD. Hipotermia seletiva do miocárdio. Rev Assoc Med Bras. 1963;9:114-6.

7. Hicks GL, Arnold W, DeWall RA. Fluorocarbon cardioplegia and myocardial protection. Ann Thorac Surg. 1983;35(5):500-3.

8. Rashid A, Jackson M, Page RD, Desmond MJ, Fabri BM. Continuous warm versus intermittent cold blood cardioplegia for coronary bypass surgery in patients with left ventricular dysfunction. Eur J Cardiothorac Surg. 1995;9(8):405-8.

9. Tönz M, Krogmann ON, Hess OM, Leskosek B, Mihaljevic T, von Segesser LK, et al. Effect of intermittent warm blood cardioplegia on functional recovery after prolonged cardiac arrest. Ann Thorac Surg. 1996;62(4):1146-51.

10. Bouchart F, Bessou JP, Tabley A, Hecketsweiller B, Mouton-Schleifer D, Redonnet M, et al. How to protect hypertrophied myocardium? A prospective clinical trial of three preservation techniques. Int J Artif Organs. 1997;20(8):440-6.

11. Carrier M, Khalil A, Tourigny A, Solymoss BC, Pelletier LC. Metabolic recovery after global myocardial ischemia: effects of blood cardioplegic solutions. Can J Cardiol. 1996;12(6):607-11.

12. McCann UG 2nd, Lutz CJ, Picone AL, Searles B, Gatto LA, Dilip KA, et al. La Cardioplegia con sangre total (minicardioplegia) disminuye el edema miocardico despues de lesió isquémica y derivación cardiopulmonar. J Extra Corpor Technol. 2006 Mar;38(1):14-21.

13. Robinson LA, Schwarz GD, Goddard DB, Fleming WH, Galbraith TA. Myocardial protection for acquired heart disease surgery: results of a national survey. Ann Thorac Surg. 1995;59(2):361-72.

14. Zornoff LAM, Cicogna AC, Paiva SAR, Spadaro J. Remodelamento e seu impacto na progressão da disfunção ventricular. Rev Soc Cardiol Estado de São Paulo. 2002;12:371-8.

15. Knobel E. Condutas no paciente grave. 3ª ed. São Paulo:Atheneu;2006. p.17-245.

16. Abduch MCD. Avaliação dos mecanismos adaptativos do miocárdio durante sobrecarga de pressão induzida com o uso de bandagem do tronco pulmonar: participação da proliferação celular [Tese de Doutorado]. São Paulo:Faculdade de Medicina da Universidade de São Paulo;2006.

17. Cicogna AC, Okoshi MP, Okoshi K. História natural da remodelação miocárdica: da agressão aos sintomas. Rev Soc Cardiol Estado de São Paulo. 2000;10(1):8-16.

18. Jessup M, Brozena S. Heart failure. N Engl J Med. 2003;348(20):2007-18.

19. Barauna VG. Participação do sistema renina-angiotensina na hipertrofia cardíaca induzida pelo treinamento resistido [Dissertação de Mestrado]. São Paulo:Escola de Educação Física e Esporte da Universidade de São Paulo;2006.

20. Martins AS, Aguilera NW, Matsubara BB, Bregagnollo EA. Experimental myocardial hypertrophy induced by a minimally invasive ascending aorta coarctation. Braz J Med Biol Res. 2001;34(3):413-5.

21. Pontes MRN, Leães PE. Remodelamento ventricular: dos mecanismos moleculares e celulares ao tratamento. Rev Soc Cardiol Rio Grande do Sul. 2004;13(3). Disponível em: http://sociedades.cardiol.br/sbc-rs/revista/2004/03/artigo11.pdf

22. Okoshi MP, Matsubara LS, Franco M, Cicogna AC, Matsubara BB. Myocyte necrosis is the basis for fibrosis in renovascular hypertensive rats. Braz J Med Biol Res. 1997;30(9):1135-44.

23. Matsubara LS, Narikawa S, Ferreira AL, Paiva SA, Zornoff LM, Matsubara BB. Remodelação miocárdica na sobrecarga crônica de pressão ou de volume no coração de ratos. Arq Bras Cardiol. 2006;86(2):126-30.

24. Matsubara LS, Matsubara BB, Okoshi MP, Cicogna AC, Janicki JS. Alterations in myocardial collagen content affect rat papillary muscle function. Am J Physiol Heart Circ Physiol. 2000;279(4):H1534-9.

25. Braile DM, Anacleto JC. Proteção miocárdica por cardioplegia. Arq Bras Cardiol. 1979;(suppl 1):19.

26. Pittella FJM. Bases metabólicas do miocárdio isquêmico-miocárdio stunned, hibernado e pré-condicionamento.Rio de Janeiro:Editorial Laranjeiras;2004. vol.1, nº 4.

27. Sant'Ana Jr O, Nogueira RJ, Murad N, Lopes AC, Tucci PJ. A depressão miocárdica pós-isquemia/reperfusão não altera a resposta cardíaca à elevação da freqüência de contrações. Arq Bras Cardiol. 2005;84(1):38-43.

28. Oliveira MAB, Godoy MF, Braile DM, Lima-Oliveira APM. Solução cardioplégica polarizante: estado da arte. Rev Bras Cir Cardiovasc. 2005;20(1):69-74.

29. Flack JE 3rd, Cook JR, May SJ, Lemeshow S, Engelman RM, Rousou JA, et al. Does cardioplegia type affect outcome and survival in patients with advanced left ventricular dysfunction? Results from the CABG Patch Trial. Circulation. 2000;102(19 Suppl 3):III84-9.

30. Buckeberg GD, Rosenkranz ER. Principles of cardioplegic myocardial protection. In: Roberts AJ, editor. Myocardial protection in cardiac surgery. New York: Marcel Dekker;1987. p.71-94.

31. Joris I, Cuénoud HF, Doern GV, Underwood JM, Majno G. Capillary leakage in inflammation. A study by vascular labeling. Am J Pathol. 1990;137(6):1353-63.

32. Braile DM, Ardito RV, Zaiantchick M, Santos JLV, Soares MJF. Cardioplegia sanguínea contínua normotérmica. Rev Bras Cir Cardiovasc. 1989;4(2):109-38.

33. Steinberg JB, Doherty NE, Munfakh NA, Geffin G, Titus JS, Hoaglin DC, et al. The addition of glucose and insulin to an oxygenated cardioplegic solution (CS). J Mol Cell Cardiol. 1990;22(suppl 5):13.

34. Thorelius J, Thelin S, Ronquist G, Haldén E, Hansson H. Creatine phosphate supplementation of cardioplegia: a clinical study. J Mol Cell Cardiol. 1990;22(suppl 5):30.

35. Palomino RS, Benites SR, Montes MM, Soto HR, Roca SM, Ruiz TI. Un análisis multifactorial de ocurrencia de arritmias al despinzamiento de aorta en las cirugías electivas de revascularización miocárdica y el uso de antiarrítmicos en la reperfusión. Rev Latinoamer Tecnol Extracorp. 2007;14(1). Disponível em: http://perfline.com/revista/volume14/v14n1/v14n1_02_art.pdf

36. Souza MHL, Elias DO. Valor prognóstico da acidose lática durante a perfusão. Rev Latinoamer Tecnol Extracorp. 2006;13(3). Disponível em: http://perfline.com/revista/

37. Wildenthal K, Mierzwiak DS, Mitchell JH. Acute effects of increased serum osmolality on left ventricular performance. Am J Physiol. 1969;216(4):898-904.

38. Dias RR, Dalva M, Santos B, Kwasnicka KL, Sarraff AP, Dias AR, et al. Influência da lidocaína na proteção miocárdica com solução cardioplégica sangüínea. Rev Bras Cir Cardiovasc. 2002;17(3):215-20.

39. Llanes Echevarria JR, Batista M, Solis M, Suárez A, Paredes A, Céspedes G, et al. Efecto de la reperfusión sanguínea normotérmica con aporte de lidocaína-magnesio, sobre el desarrollo de fibrilación ventricular, en el período post-paro anóxico de la cirugía coronaria y valvular, con circulación extracorpórea. Rev Latinoamer Tecnol Extracorp. 2006;13(2):12-6.

40. Rosenkranz ER, Vinten-Johansen J, Buckberg GD, Okamoto F, Edwards H, Bugyi H. Benefits of normothermic induction of blood cardioplegia in energy-depleted hearts, with maintenance of arrest by multidose cold blood cardioplegic infusions. J Thorac Cardiovasc Surg. 1982;84(5):667-77.

41. Elias DO, Souza MHL. Injúria e proteção do miocárdio em neonatos. Rev Latinoamer Tecnol Extracorp. 2004;11(2). Disponível em: http://perfline.com/revista/volume11/v11n2/v11n2-04.html

42. Vinten-Johansen J, Chiantella V, Faust KB, Johnston WE, McCain BL, Hartman M, et al. Myocardial protection with blood cardioplegia in ischemically injured hearts: reduction of reoxygenation injury with allopurinol. Ann Thorac Surg. 1988;45(3):319-26.

43. Schneider CD, Oliveira AR. Radicais livres de oxigênio e exercício: mecanismos de formação e adaptação ao treinamento físico. Rev Bras Med Esporte. 2004;10(4):308-13.

44. McCord JM, Fridovich I. Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein). J Biol Chem. 1969;244(22):6049-55.

45. Lopes AC. Tratado de clínica médica. v. 2. São Paulo:Roca;2006.

46. Teoh LK, Grant R, Hulf JA, Pugsley WB, Yellon DM. A comparison between ischemic preconditioning, intermittent cross-clamp fibrillation and cold crystalloid cardioplegia for myocardial protection during coronary artery bypass graft surgery. Cardiovasc Surg. 2002;10(3):251-5.

47. Luo WJ, Qian JF, Jiang HH. Pretreatment with aminophylline reduces release of Troponin I and neutrophil activation in the myocardium of patients undergoing cardioplegic arrest. Eur J Cardiothorac Surg. 2007;31(3):360-5.

48. Buckberg GD. A proposed "solution" to the cardioplegic controversy. J Thorac Cardiovasc Surg. 1979;77(6):803-15.

49. Lima-Oliveira APM, Azeredo-Oliveira MTV, Taboga SR, Godoy MF, Braile DM. Cardioplegia utilizando baixo volume de agentes cardioplégicos: estudo morfológico em coração isolado de coelhos. Rev Bras Cir Cardiovasc. 2003;18:227-34.

50. Cressoni ES, Avanci LE, Braile DM, Lima-Oliveira APM, Taboga SR, Martins AS, et al. Efeitos das cardioplegias sangüínea e cristalóide no miocárdio hipertrófico de coelho: avaliação estrutural e ultra-estrutural. Rev Bras Cir Cardiovasc. 2007;22(1):24-32.

51. Martins AS, Silva MA, Padovani CR, Matsubara BB, Braile DM, Catâneo AJ. Proteção miocárdica da cardioplegia sanguínea contínua, anterógrada e retrógrada em coelhos. Acta Cir Bras. 2007;22(1):43-6.

52. Sobrosa CG, Jansson E, Kaijser L, Bomfim V. Metabolismo miocárdico após cardioplegia sangüínea hipotérmica retrógrada contínua com indução anterógrada normotérmica. Rev Bras Cir Cardiovasc. 2005;20(4):416-22.

53. Bothe W. Retrograde administration. Multimidia manual of cardiothoracic surgery. (9 de Agosto, 2005) 809:711.

54. Bel A, Aznag H, Faris B, Menasché P. Warm blood cardioplegia in high risk patients. Eur J Cardiothorac Surg. 1997;11(6):1118-23.

55. Foglia RP, Partington MT, Buckberg GD, Leaf J. Iatrogenic myocardial edema with crystalloid primes. Effects on left ventricular compliance, performance, and perfusion. Curr Stud Hematol Blood Transfus. 1986;(53):53-63.

56. Évora PR, Pearson PJ, Discigil B, Oeltjen M, Schaff HV. Efeito protetor da criocardioplegia cristalóide na isquemia global e reperfusão durante circulação extracorpórea: um mecanismo dependente do endotélio? Rev Bras Cir Cardiovasc. 1997;12(1):68-76.

57. Chemnitius JM, Burger W, Bing RJ. Crystalloid and perfluorochemical perfusates in an isolated working rabbit heart preparation. Am J Physiol. 1985;249(2 Pt 2):H285-92.

58. Nappi G, Torella M, Romano G. Clinical evaluation of normothermic cardiopulmonary bypass and cold cardioplegia. J Cardiovasc Surg. 2002;43(1):31-6.

59. Martins AS. Análise comparativa entre dois métodos de proteção miocárdica: cardioplegia cristalóide, intermitente e fria e cardioplegia sanguínea, contínua tépida. Estudo experimental em coelhos [Tese de Doutorado]. Botucatu: Faculdade de Medicina de Botucatu, Universidade Estadual Paulista Júlio de Mesquita Filho;1998. 170p.

60. Godoy MF, Braile DM. Cardioplegia: exegese. Arq Bras Cardiol. 1994;62:277-8.

61. Kuznetsov SV, Gritsenko VV, Doinikov DN, Mochalov OI, Sharafutdinov VE. Experience in the use and comparative assessment of the effectiveness of crystalloid and blood cardioplegia. Vestn Khir Im I I Grek. 2001;160(5):52-4.

62. Braile DM, Ardito RV, Thevenard GHP, Ramin SL, Silva EM. Cardioplegia sanguínea normotérmica na revascularização cirúrgica do miocárdio. Rev Soc Cardiol Estado de São Paulo. 1991;1:26-37.

63. Martins AS. Modelo experimental de coração suportado em coelhos: padronização e análise de variáveis hemodinâmicas, laboratoriais e anatomopatológicas [Tese de Mestrado]. Botucatu: Faculdade de Medicina de Botucatu, Universidade Estadual Paulista Júlio de Mesquita Filho;1996. 242p.

64. Martins AS, Matsubara BB, Braile DM, Gomes OM. Proteção miocárdica e função ventricular. Botucatu:Cultura Acadêmica Editora;2004. p.262.

65. Rao PV, Johnson JM, Forsyth AT. A simple, safe and economical method for administration of continuous warm blood cardioplegia. Perfusion. 1994;9(4):285-7.

66. Gomes WJ, Ascione R, Suleiman MS, Bryan AJ, Angelini GD. Efeitos das cardioplegias sanguíneas hipotérmica e normotérmica nos substratos intracelulares em pacientes com corações hipertróficos. Rev Bras Cir Cardiovasc. 2000;15(2):160-8.

67. Godoy MF, Braile DM, Purini Neto J. A troponina como marcador de injúria celular miocárdica. Arq Bras Cardiol. 1998;71(4):629-33.

68. Mair J, Larue C, Mair P, Balogh D, Calzolari C, Puschendorf B. Use of cardiac troponin I to diagnose perioperative myocardial infarction in coronary artery bypass grafting. Clin Chem. 1994;40(11 Pt 1):2066-70.

69. Thormann J, Schlepper M. Comparison of myocardial flow, hemodynamic changes, and lactate metabolism during isoproterenol stress in patients with coronary heart disease and severe aortic stenosis. Clin Cardiol. 1979;2(6):437-45.

70. Braile DM. Como eu faço: cardioplegia sanguínea isotérmica retrógrada de baixo volume. Rev Bras Cir Cardiovasc. 1992;7:221-9.

71. Braile DM. Cardioplegia isotérmica anterógrada retrógrada de baixo volume. 2ª ed. São José do Rio Preto;1997. p.53.