

# Myocardial protection to the hypertrophied heart: the eternal challenge

*Proteção miocárdica ao coração hipertrofiado: o eterno desafio*

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## *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.

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### 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 morbidity 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 cardioplegia, 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 (sympathetic, 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 sarcolemma 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), TGF $\beta$  1, proinflammatory cytokines (e.g., TNF- $\alpha$ ), 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 extracellular 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 light chains
Calcium transit	Calcium channel alterations Calmodulin SR-Ca <sup>++</sup> -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, identifying 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).

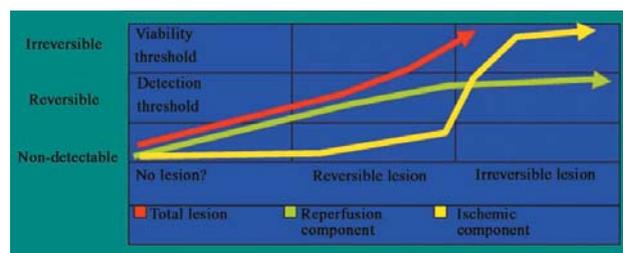


Fig. 1 – Myocardial evolutionary impairment resulting from ischemia reperfusion or complete occlusion

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, hyperosmolar 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 beginning of cardiopulmonary bypass significantly reduced the oxidative lesion and myocardial dysfunction extension [43].

The studies carried out by McSord & Fridovich [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<sup>+</sup> 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 (30°C), 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 cardioplegia 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 and 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 these 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<sup>+</sup>/K<sup>+</sup> 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 mitochondrion 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 4° to 7°C; it is aimed a temperature between 12° and 18°C, 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 sufficient 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 sufficient 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; insulin 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 <sup>++</sup>	30	0.5 - 0.6 mM/l
Potassium chloride	K <sup>+</sup>	20	22 - 24 mEq/l
Sodium bicarbonate	pH	8	7.5 - 7.6 mEq/l
Magnesium sulfate	Mg <sup>++</sup>	10	4.4 - 5.2
Simple insulin	Substrate	10 IU	2.0 IU/l
Papaverine	Ca <sup>++</sup>	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 sufficient 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 sinus 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.

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