REVIEW ARTICLE

Braz J Cardiovasc Surg 2005; 20(1): 69-74

Polarizing cardioplegic solution: state of the art

Solução cardioplégica polarizante: estado da arte

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RBCCV 44205-732

Abstract

The meaning of the term "cardioplegia" is "lesion, attack, wound or blow", very different to how it is most commonly understood in most heart centers, where it relates to cardiac protection. Thus, "cardioplegic solution" is better defined as a solution capable of inducing controlled cardiac arrest. Cardiac arrest induced by cardioplegic solutions can occur by hyperpolarization, depolarization or by inhibiting the calcium channels of the myocardial fibers. This paper discusses hyperpolarizing cardioplegic solutions, which arrest the heart in the diastolic phase, thus decreasing the ATP depletion and improving the conditions of the heart to be reanimated at the end of the procedure.

***Descriptors*: Cardioplegic solutions. Heart arrest, induced. Myocardium, metabolism.**

Resumo

A exegese do termo cardioplegia remete aos significados de "lesão, golpe, ataque ou ferimento", bem diferente, portanto, do sentido em que o termo é empregado na maior parte dos centros de cirurgia cardíaca do Brasil e do mundo, ou seja, como correspondendo à proteção miocárdica. Daí a melhor denominação de solução cardioplégica, para caracterizar as soluções empregadas com finalidade de promover a parada cardíaca controlada do coração. A parada cardíaca induzida por solução cardioplégica pode acontecer por hiperpolarização, despolarização ou com bloqueadores da bomba de cálcio. No presente trabalho, discorreremos sobre os principais agentes que promovem a parada cardíaca por hiperpolarização da membrana miocárdica. Com a solução hiperpolarizante, o coração pára no período diastólico, havendo uma redução ainda maior no seu gasto energético, o que propicia melhores condições ao coração quando este reinicia sua contração ao final do procedimento cirúrgico.

***Descritores:* Soluções cardioplégicas. Parada cardíaca induzida. Miocárdio, metabolismo.**

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Article received in March, 2004
Article accepted in January, 2005

INTRODUCTION

The term cardioplegia, which literally means the arrest or paralysis of the heart, has an occult significance based on the exegesis of the term corresponding to aggression, attack or injury of the heart. This is much different to the general concept that seems to automatically link cardioplegia to myocardial protection [1]. Indeed, myocardial protection can be obtained using cardioplegic solutions with added substrates or elements that make the desired protection possible.

The development of protection and myocardial resuscitation methods have quickly and continuously evolved over the last few years, mainly due to the establishment of a fundamental understanding of the cardiac metabolism and of techniques that allow their use in an efficient and practical manner.

Elective cardiac arrest can be achieved using a wide range of substances that provoke depolarization, polarization or that act on the calcium channels.

Cardiac arrest by depolarization (using solutions rich in potassium), has already been extensively studied by several authors and this is, by far, the most commonly used method today. But this technique has a series of disadvantages, including the opening of slow calcium channels, increasing the concentration of calcium in the intracellular space, with a depletion of ATP (adenosine triphosphate) and the activation of the programmed cell death mechanisms and reperfusion lesions [2-4].

The goal of the current paper is to review the literature about alternative forms of elective cardiac arrest that cause polarization of the myocardial membrane, thereby attempting to minimize energy consumption during cardiac arrest.

Polarized cardiac arrest

An alternative to cardiac arrest is to maintain the polarity of the membrane similar to the potential at rest. A polarized arrest has a series of advantages, including a reduction of the ionic movement (particularly Na^+ and Ca^{++}), as, when there is no ionic movement, there is no energy consumption [5]. Polarized arrest can be achieved in many ways, including:

Sodium channel Blockers

Obstruction of the sodium channels can effectively arrest the heart, preventing the 0 phase (fast depolarization) of the cardiac cycle [6].

Local anesthetic agents such as lidocaine and procaine have already been used with other agents for the induction of cardiac arrest [2]. Procaine is part of the St. Thomas cardioplegia solution used to stabilize the membrane and has provided benefits including decreasing the occurrence of arrhythmias and other rhythm disorders [7]. There is, however, a considerable risk of convulsions in the postoperative period [8,9].

Tetrodoxine (TTX), another sodium channel blocker, is highly toxic but it has been proved to be very efficient to reverse cardiac arrest and is better than hyperkalemic arrest due to the reduction of energy consumption and the more physiological state of rest [7,l0].

Alternatively, the maintenance of the myocardial membrane potential at around –80 mV, in polarized or hyperpolarized states, has many advantages, because, at this level, the voltage-dependent channels remain inactive. In addition, the metabolic demand decreases on account of the balanced potential.

Induction by polarized arrest achieved, for example, using TTX, a specific sodium channel blocker, results in significant myocardial protection during normothermic ischemia [11,12] and reduces the myocardial oxygen consumption when compared with hyperkalemic arrest [10]. However, the polarity of the myocardial membrane during ischemia was not determined in any of these studies.

The idea to use TTX is not new. TYERS et al. [11,12] were the first to demonstrate the cardioprotector effects of TTX, during experimental cardiac arrest in rat hearts using a cardioplegia solution containing this component in the middle of the 1970s. These authors concluded that at least 14 μg of intracoronary TTX (7 μg/mL; 22 μmol/L) would be necessary to induce cardiac arrest.

The advantage of arrest with normal polarity or hyperpolarization is that the calcium channels are not activated [13] so that oxygen consumption is reduced to a minimum [10].

Cardiac arrest using an optimum TTX concentration (22 μmol/L) significantly improves the post-ischemic myocardial recovery of rat hearts maintained for five hours at an optimum temperature (7.5 ºC), when compared with hearts arrested by conventional techniques using hyperkalemic solutions with 16 mmo1/L or ischemic arrest. It was also demonstrated that hyperpolarized arrest leaves the membrane with the potential of approximately –70 mV, in comparison with depolarized arrest, which occurs at a potential of approximately –50 mV [14].

Previous studies have demonstrated that arrest by TTX gave better ATP and creatine phosphate levels after ischemia and reperfusion, when compared with hearts subjected to non-protected ischemia [12] or even those protected by K^+ rich solutions [14].

Depolarization dependent on potassium, elevates intracellular calcium by means of voltage-dependent calcium channels, with an increase in energy consumption [10].

Activation of the ATP-sensitive potassium channels

There are dramatic changes in the action potential during

myocardial ischemia. There is a decrease in the resting potential of the membrane (depolarization) and in the action potential and shortening of the duration of the action potential [15-18]. Many of these electrophysiological changes occur because of the efflux of intracellular potassium [15].

NOMA [20] described a specific potassium channel in ventricular myocytes of guinea pigs and rabbits, which was inhibited by intracellular ATP and opened during periods of ischemia. The opening of this ATP-sensitive channel causes a potassium outflow from the cell that hyperpolarizes the membrane. This channel is responsible for many of the myocardial responses to ischemia [18,20,21], particularly the marked shortening of the action potential. This results in a reduction of the plateau phase, which is the phase in which the majority of the calcium enters. This reduction in calcium inflow causes a decrease in the contractility. The activation of these receptors explains the occurrence of contractile dysfunction in long periods of ischemia and metabolic inhibition [22]. This decrease in the mechanical activity saves energy and ATP and thus it acts as a cardioprotector during ischemia [19].

A pharmacological activation of the ATP-dependent potassium channels proved to be able to protect the myocardium in several animal models with myocardial ischemia [21,23-27]. The benefits include preservation of the ventricular function and the activity of high-energy nucleotides, as well as limiting of the grade of post-ischemic infarction. These channels also play a significant role in the ischemia preconditioning phenomenon and also cause relaxation of the smooth muscles and are therefore potent vasodilators [28,29].

Adenosine

Adenosine can also induce cardiac arrest by its hyperpolarizing effect, particularly on conduction tissue [30] which has proved to provide good myocardial protection, when used alone as a cardioplegic agent (in concentrations of 10 mmol/L) [31,32] or when added (1 mmol/L) to cardioplegic solutions with potassium [33].

This has been shown to reduce the arrest time and to be more efficient than hyperkalemic arrest alone, decreasing the overload of calcium in isolated myocytes [34].

More recently, the beneficial effect of adenosine (for cardioplegia with hyperpotassemia) was clinically tested and this substance proved to be safe, reducing postoperative complications [35].

The association of adenosine with lidocaine, both of which induce hyperpolarized arrest, was seen to have an efficient protector effect for periods of ischemia greater than 4 hours [36].

Hypocalcemia

The absence of intracellular calcium provokes cardiac arrest in diastole, inhibiting the excitation-contraction coupling [37]. This characteristic has been used in cardioplegic solutions in Germany for some time however when it is accompanied with hyponatremia it also reduces the sodium channel function, maintaining the membrane potential close to the resting potential. However, the absence of the calcium increases the risk of inducing the "calcium paradox". Traces of calcium with hypothermia and hyponatremia or contaminating hypermagnesemia protect against this phenomenon. An alternative manner to block the activity mediated by calcium is through the use of drugs that inhibit its movement [38].

Calcium antagonists

High concentrations of calcium antagonists prevent increases of this ion in the interior of the myocytes and cause cardiac arrest by inhibiting the excitation-contraction coupling. Potentially, this causes myocardial protection comparable to hyperkalemic arrest, but recovery of the myocardial contractility is slow. Thus, it is not recommendable to utilize this in isolation, but its safety increases when used as a "constituent" of hyperkalemic cardioplegic solution. Its effects are dependent on the temperature, with a small benefit when used in hypothermia [39].

Hypermagnesemia

Hypermagnesemia can arrest the heart, probably by displacing calcium from receptors in the sarcolem involved in heart contraction [40]. However, it is less efficient than hyperpotassemia and requires a higher concentration [2].

Similar to calcium channel antagonists, hypermagnesemia is efficient in cardioplegic solutions and is used in the St. Thomas solution at a concentration of 16 mmol/L [41].

Butanedione Monoxime (BDM)

BDM is an efficient, quick and completely reversible inhibitor of muscular contraction in man, both for the skeletal musculature and heart muscles [42].

Its action was correlated to a reduction in reperfusion injury when added to cardioplegic solutions in several experimental animal isolated heart models investigating ventricular recuperation [43-45].

Its use during reperfusion in the preparation of the Langendorff system also gave a better myocardial functioning, but the problem of the systemic effects of the drug has still to be resolved [46]. As an adjunct agent in cardioplegia, no adverse effect has been described.

Esmolol

Esmolol, an ultra-rapid beta blocker with a half life of 10 minutes, was used during heart surgery to induce minimal myocardial contraction, while maintaining a continuous normothermic perfusion to avoid ischemia and it proved to be a myocardial protector equivalent to cardioplegia [47].

At high concentrations (approximately 1.0 mmol/L), it is capable of inducing cardiac arrest [48,49]. Several infusions of solutions with 1.0 mmol/L of esmolol (for 2 minutes at 15 to 45 mmHg) gave total protection to rat hearts submitted to crystalloid cardioplegia over periods of more than 90 minutes at normothermia [49,50].

CONCLUSION

Cardiac arrest by hyperpolarization of the myocardial membrane is a technique still not routinely utilized in many cardiac centers, but it can provide some answers to problems seen in conventional cardioplegia such as the energy consumption with the cytoplasmatic inflow of calcium. Moreover, it brings new problems that still need to be solved, such as the ideal concentration of its constituents. Thus, only future works will prove that it is a safe and reproducible method for routine use in the surgical center.

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