

Del Nido cardioplegia – what is the current evidence?

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Abstract

Del Nido cardioplegia is believed to be both clinically and economically efficient. The interest in this myocardial protection method has been continuously growing. However, the evidence is not clear. The article summarizes recent reports regarding del Nido cardioplegia.

Key words: del Nido, cardioplegia.

Introduction

Cardiac surgery procedures usually involve the use of cardiopulmonary bypass and cardiac arrest. In consequence, myocardial protection is essential. Inadequate protection may cause myocardial stunning, cell apoptosis and infarction.

The search for an ideal cardioplegic solution has continued since the very beginning of cardiac surgery. Plenty of solutions are available, both commercial and self-made. Yet, there are no guidelines referring to use of a specific solution, and the literature does not clearly confirm the superiority of one over another.

Mechanism of myocardial injury

The understanding of ischemia-reperfusion injury by practicing cardiac surgeons plays the key role in the myocardial protection strategy and may be one of the main determinants of clinical outcome. The damage is induced while the heart is arrested. However, it is aggravated during the reperfusion (the "ischemia-reperfusion injury"). Free oxygen radicals and calcium ions are the most important factors determining the injury progression [1, 2]. Cessation of the oxygen supply has its consequence in a loss of ATP production and an increase of reactive oxygen species in the mitochondria. The Na⁺-K⁺-pump's activity is strictly related to ATP availability. Its dysfunction leads to Na⁺ accumulation in the cell. In consequence, the

Streszczenie

Kardioplegina del Nido jest uznawana za roztwór o dużej skuteczności klinicznej, który zapewnia optymalną efektywność kosztową. Wydaje się, że ciągle wzrasta zainteresowanie jej stosowaniem. Dotychczasowe badania nie są jednak jednoznaczne. W artykule przedstawiono ostatnie doniesienia dotyczące stosowania kardiopleginy del Nido.

Słowa kluczowe: del Nido, kardioplegia.

membrane potential is lowered. The anaerobic metabolism for ATP production proceeds, resulting in gathering of hydrogen ions and lactate, which decreases anaerobic glycolysis.

As acidosis progresses, the Na⁺-H⁺ exchanger leads to further intracellular Na⁺ accumulation. The 3 Na⁺-1 Ca²⁺ exchanger function deteriorates because of the Na⁺ increase. It may work in the reverse mode as well. Both mechanisms lead to intracellular Ca²⁺ gathering. The other mechanism of intracellular Ca²⁺ accumulation is its release from the sarcolemmal L-type voltage-gated Ca²⁺ channel (L) as a consequence of lowering the resting membrane potential. Furthermore, the mitochondrial calcium uptake is damaged due to ischemic depolarization and impaired recovery of membrane potential during reperfusion.

The Na⁺-K⁺ pump recovers slowly due to ATP production in the reperfusion process. The reoxygenation triggers reactive oxygen species formation. Moreover, an elevated level of Ca²⁺ in this early phase of reperfusion, when compensatory mechanisms are not efficient, causes myocardial hypercontracture and severe myocardial damage. The Ca²⁺ ions are currently believed to be the most important factor in ischemia-reperfusion injury [3].

The cardioplegia concept

In 1950 Bigelow *et al.* opened the pathway for further development of surgical myocardial protection by describ-

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ing the application of deep hypothermia in canines [4]. Three years later Melrose *et al.* introduced the concept of chemical cardiac arrest in canines [5]. Gerbode and Melrose were the first to report use of potassium citrate to induce cardiac arrest in humans [6]. The project relied on the assumption that a high concentration of potassium ions depolarizes the membrane and arrests the heart in diastole. This publication began the era of cardioplegia.

In general, two types of cardioplegia are described:

1. Cold crystalloid cardioplegic solutions

They contain potassium concentration in the range between 10 and 40 mmol/l (mEq/l) and usually have high buffering capability (bicarbonate). There are various types of solutions, both commercial and self-made. They may be further divided into two types.

– Intracellular type – typically characterized by absent or low concentrations of sodium and calcium.

– Extracellular type – typically characterized by higher concentrations of sodium, calcium and magnesium.

2. Blood cardioplegia

– Cold blood cardioplegia – probably the most widely used solution across the globe. There are various formulations. Autologous blood from the cardiopulmonary circuit is obtained and mixed with crystalloid solution. A high concentration of potassium (> 30 mEq/l) is used for arresting the heart. Potential additives include, for example, citrate-phosphate-dextrose (CPD), tris-hydroxymethyl aminomethane (THAM) or bicarbonate. The most common blood : crystalloid ratio is 4 : 1 or 8 : 1. The delivery temperature is 4–12°C.

– Warm blood cardioplegia – usually delivered additionally to another cardioprotective method as a “hot shot”

(single administration just before declamping the aorta), which is intended to improve myocardial recovery.

– Tepid blood cardioplegia – originally described as 29°C cardioplegia. In some studies, it revealed excellent capabilities in reducing anaerobic lactate acid release [7]. Its role has not been confirmed in a large, multicenter study.

Del Nido cardioplegia

Del Nido cardioplegia was developed by Pedro Del Nido and his team at the University of Pittsburgh in 1990s. It has been used for pediatric cardiac surgery in Boston's Children Hospital since 1994 and, since 2003, it has been successfully used for adult cardiac surgery as well [8].

The cardioplegia solution itself is an extracellular solution mixed with autologous blood obtained from the extracorporeal circuit. The crystalloid : blood ratio is 4 : 1. One dose of 20 ml/kg is calculated to obtain optimal myocardial protection for 90 min. The administration pressure is 100–200 mm Hg and the administration flow is 200–300 ml/min. The potassium concentration is > 25 mEq/l. The achieved myocardial temperature is < 15°C. The crystalloid solution includes Plasma-Lyte as a basic solution, mannitol, magnesium sulfate, bicarbonate, potassium and lidocaine (Table I). Some ingredients have a different concentration and volume when distributed in Europe, so the formula needs to be modified (as seen in Table II) to obtain the same ingredient concentration in the solution.

Each ingredient plays an important role in the cardioprotection strategy. Plasma-Lyte A is a commercial solution. It contains 140 mEq/l sodium, 5 mEq/l potassium, 3 mEq/l magnesium, 98 mEq/l chloride, 27 mEq/l acetate and 23 mEq/l gluconate. The pH is 7.4.

Table I. The del Nido cardioplegia solution as described originally

Ingredient	Volume [ml]	Role
Plasma-Lyte A	1000	Basic solution (Na 140 mmol/l; K 5 mmol/l; Mg 3 mmol/l; pH 7.4)
Mannitol 20%	16.3	Osmotic pressure, free-radical scavenger
MgSO ₄ 50%	4	Calcium channel blocker, improved myocardial recovery
NaHCO ₃ 8.4%	13	pH buffer
KCl 2 mEq/l	13	Myocardial depolarization
Lidocaine 1%	13	Sodium channel blocker, hyperpolarizing agent

Table II. The del Nido cardioplegia solution – calculated for European products

Ingredient	Volume [ml]	Role
Plasma-Lyte A	1000	Basic solution (Na 140 mmol/l; K 5 mmol/l; Mg 3 mmol/l; pH 7.4)
Mannitol 15%	20	Osmotic pressure, free-radical scavenger
MgSO ₄ 20%	10	Calcium channel blocker, improved myocardial recovery
NaHCO ₃ 1 mEq/ml	13	pH buffer
KCl 2 mEq/l	13	Myocardial depolarization
Lidocaine 2%	6.5	Sodium channel blocker, hyperpolarizing agent

Mannitol has capabilities of both scavenging free radicals and reducing edema due to its hyperosmotic capabilities [9].

Magnesium additive blocks the calcium channels [10], which has proved to improve myocardial recovery [11, 12].

Sodium bicarbonate scavenges hydrogen ions and maintains intracellular pH.

Potassium chloride provides rapid depolarized arrest. However, research associates sole depolarized arrest with impaired myocardial recovery due to intracellular sodium and calcium accumulation [13]. The potassium concentration in the del Nido cardioplegia solution is 24 mEq/l.

Lidocaine is a sodium channel blocker and class Ib antiarrhythmic agent. It increases the myocyte refractory period [14]. It prevents the negative effect of hyperkalemic depolarized arrest by polarizing the cell to some degree and reducing intracellular sodium and calcium influx [15].

The crystalloid del Nido solution is given with 20% volume blood additive. The blood has its effect in supporting aerobic metabolism, providing buffering capabilities and improving coronary perfusion during the delivery [16]. Some reports prove blood cardioplegia to be excellent in preserving myocardial metabolism and reducing ischemic stress along with reperfusion injury [17, 18]. What is important, the blood addition is the only source of calcium ions in the del Nido cardioplegia solution. This ensures that only a trace of calcium is given. The delivery temperature is 8–12°C. The hypothermia reduces metabolism and oxygen consumption [14, 19].

In 2012 Matte, who is a clinical perfusion coordinator at Boston Children's Hospital, and del Nido himself described the aspects of using the cardioplegia at their institution in detail. The history, supporting theories and the protocols at the facility are discussed, which makes the publication a great reference for everyone who is interested in launching the del Nido cardioplegia protocol at their hospital [8].

Animal studies

Del Nido cardioplegia has been deeply analyzed in both animal and human studies. In 2013 Govindapillai conducted a study in isolated rat hearts. He proved that del Nido cardioplegia is superior to blood cardioplegia in old hearts when spontaneous contractions during ischemia, troponin release and stroke work are taken into account [20]. The same author reported that single dose del Nido cardioplegia is superior to multidose del Nido cardioplegia in aged rat hearts (functional recovery was measured after 60 min of cardioplegic arrest) [21].

Pediatric patients

The first clinical study referring to del Nido cardioplegia was conducted in Halifax by O'Brien in 2009. It proved that del Nido cardioplegia results in lower troponin T and better calcium management as compared to their institutional standard cardioplegia in pediatric patients [22].

Charette *et al.* carried out a clinical investigation in a group of 34 pediatric patients. Each patient had a cross-

clamp time longer than 90 min and was given either single-dose del Nido cardioplegia or modified adult multidose cardioplegia solution. There were no significant differences between the groups in the risk adjustment for congenital heart surgery, cardiopulmonary bypass times, aortic cross clamp times, weights or number of intraoperative exogenous blood units. The authors report that there were significant differences between the groups in the number of cardioplegia doses and in perioperative glucose levels [23].

Reports from pediatric cardiothoracic surgeons in North America described a single shot of del Nido cardioplegia solution to be the most commonly used cardioprotective strategy (38%), regardless of cross-clamp time [24].

Del Nido cardioplegia was compared with St Thomas cardioplegia in pediatric patients in a randomized trial. The study included 100 pediatric patients ≤ 12 years undergoing elective repair of ventricular septal defects and tetralogy of Fallot. A single dose of del Nido solution or 30-minute interval repeat St Thomas solution was administered. Apart from clinical parameters, myocardial biopsy was obtained to assess electron-microscopic ultrastructural changes. The cardiac index was on average 0.50 l/min/m² higher in the del Nido group than in the St Thomas group at any time point (2, 6 and 24 h). Mechanical ventilation, intensive care unit stay and hospital stay were significantly lower in the del Nido group. The group also had lower troponin-I release at a 24-hour interval. Electron microscopic studies showed more myofibrillar disarray in the St Thomas solution group [25]. Another pediatric study that included those cardioplegic solutions in pediatric patients indicated a decrease in the rate of defibrillation post cross-clamp removal in all weight categories in the del Nido group [26].

The del Nido cardioplegia and modified St Thomas solution cardioplegia were compared in a randomized control trial in terms of inflammatory cytokine response and cardiac troponin I changes. The patients underwent tetralogy of Fallot surgery. No significant differences in TNF- α , IL-6 or IL-8 cytokines levels were reported. IL-10 level showed a moderately significant increase in the St Thomas solution group. Postoperative lactate level was significantly higher in the del Nido group. Differences in troponin levels were not detected. The authors concluded that anti-inflammatory cytokine response in the St Thomas solution group is significantly better than in the del Nido group, which may be due to shorter intervals of the St Thomas solution administration [27].

Adult patients

The comparison between del Nido and St Thomas No. 2 solution was conducted in adult patients as well. The study included 100 patients who underwent coronary artery bypass grafting or double valve replacement. The aortic cross clamp and bypass times were shorter in the del Nido group. In this study the postoperative left ventricular ejection fraction was better preserved in the del Nido group [28].

Smigla *et al.* studied 47 consecutive adult patients (mean age: 40.9 years, range: 18–71), who received the del

Nido cardioplegia for congenital surgery. According to the protocol, an additional dose of cardioplegia was given every 45 min. In patients who received a single dose ($n = 19$), the cross-clamp time was 49.8 ± 18.8 min. The patients demonstrated no ventricular electrical activity while the aorta was cross-clamped. Post-operative ECHO showed that 94% had no change in ejection fraction from the pre-operative ECHO. However, 43% of patients needed inotropic support while leaving the OR. The average post-operative troponin T level was $1.86 \pm 2.9 \mu\text{g/l}$ [29].

Among propensity matched adult patients undergoing aortic or mitral surgery, who received either del Nido or Buckberg cardioplegia solution, troponin level and postoperative ejection fraction did not differ. Aortic clamp, bypass, and operating room times were shorter in the del Nido group. Peak glucose level and insulin requirements were also lower in this group [30].

Ramanathan retrospectively studied cases of 142 adult patients (valvular, aortic and bypass procedures) who received either del Nido or Buckberg cardioplegia. In this publication, fewer doses of cardioplegia and fewer defibrillations were noted in the del Nido group and there were no significant differences in incidence of postoperative events [31].

In a short-term analysis of adult patients who underwent aortic valve surgery (retrospective study) and were given either del Nido or conventional whole blood cardioplegia, mean cardiopulmonary bypass time and mean aortic cross-clamp time were significantly shorter in the del Nido group. Postoperative inotropic support was required in 20.4% of patients in the del Nido group and 24.1% of patients in the conventional group, with no significant difference. There was no significant difference in postoperative complications between the two groups [32].

The analysis of adult patients undergoing minimally invasive aortic valve surgery included 178 patients. Blood cardioplegia patients received both antegrade and retrograde cardioplegia in multiple doses while single-dose del Nido was delivered almost entirely antegradely. The del Nido cardioplegia use was associated with decreased cardiopulmonary bypass time and aortic-cross clamp time. Maximal glucose level during cardiopulmonary bypass was lower in the del Nido group, while troponin T level and ejection fraction did not differ between the groups [33]. Another study reports a lower rate of ventricular fibrillation at unclamping and lower postoperative creatinine kinase-MB (CK-MB) values in the del Nido group with less postoperative use of intravenous insulin [34].

Coronary artery bypass surgery was proven to be safe with del Nido cardioplegia, as patients had similar results but required less defibrillation and blood transfusion when compared to blood cardioplegia [35]. Another study reported lower glucose levels during cardiopulmonary bypass [36].

Redo surgery is usually associated with longer cross-clamp and cardiopulmonary bypass times. Sorabella *et al.* investigated del Nido cardioplegia use in adult reoperative aortic valve surgery. This included 113 patients divided into del Nido and blood cardioplegia groups. There were no dif-

ferences in cross-clamp time, bypass time, postoperative complication rate, or patient outcomes between groups [37].

The adequate myocardial protection of del Nido cardioplegia regardless of ventricular mass and myocardial ischemic time in adult cardiac surgical patients was reported by Kim *et al.* In this study, spontaneous defibrillation was achieved more frequently in the del Nido group when compared to blood cardioplegia groups. Peak level and serial changes of Tnl were not significantly different between the two groups [38].

In a propensity matched trial (CABG + valve patients) Loberman *et al.* reported similar clamp and cardiopulmonary bypass time in both del Nido and whole blood cardioplegia groups. However, the del Nido group had higher CK-MB levels at 24 h, but lower incidence of postoperative atrial fibrillation [39].

Conclusions

The literature is encouraging – the del Nido cardioplegia solution appears to be highly efficient in both myocardial protection and economic aspects. However, there are only a few randomized trials in pediatric patients and no randomized trials in adult patients. Most of them are retrospective or propensity matched, which makes their value limited. It is necessary to conduct a prospective, randomized trial to prove the hypothesis of feasibility or superiority of this cardioplegia over another in terms of myocardial protection.

Disclosure

Authors report no conflict of interest.

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