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Review

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Historical Aspects of the Application of a Cardioplegic Solution Del Nido

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ABSTRACT Cardioplegia is an integral and important method of myocardial protection in patients of all ages requiring cardiac surgery in which cardiac arrest is necessary. Numerous solutions and delivery methods have been developed. Del Nido solution has been used for 30 years at Boston Children's Hospital. It is a unique solution consisting of four parts crystalloid and one part whole blood that is typically used in a single dose. Although the drug was originally developed for use in pediatrics and infants, its use in adult cardiac surgery has recently been expanding.

Keywords: cardioplegia, Del Nido

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INTRODUCTION

Initially, cardioplegia for infants and pediatric patients was the same as for adults, simply adjusted for volume, flow, and pressure [1, 2]. Plegisol cardioplegic solution (Abbott Laboratories, Chicago, IL) was widely used in the 1980s and 1990s [3]. Researchers at the University of Pittsburgh recognized the need to create a cardioplegic solution that would better suit the needs and characteristics of the immature heart. The differences and requirements of the immature myocardium were described inconsistently, with the immature heart characterized as more tolerant to ischemia [4–6] and less tolerant to ischemia [7, 8]. A 1989 study by Kempsford and Hearse [9] may explain this controversy by suggesting that the effectiveness of cardioplegia in immature myocardium may be more related to the cardioplegic solution than to the physiology of the neonatal heart. However, controversies persist: St. Thomas solution may be effective [10, 11] or ineffective [7] in the neonatal heart. Moreover, single-dose cardioplegia was shown experimentally to be superior to multi-dose cardioplegia in neonatal hearts [10, 12, 13], while other researchers found no difference when compared with multi-dose cardioplegia [14]. The controversies are to be expected in the studies cited, as they were all conducted in animal models with different and/or uncertain delivery protocols. During the development of cardioplegia, the researchers at the University of Pittsburgh focused on increasingly sophisticated and precise measurements of intracellular calcium levels and its regulation, myocardial high-energy phosphates such as adenosine triphosphate (ATP), lactate production, and intracellular buffering. Although many concepts were developed on rodent models, the efficacy of protection and applicability to animal hearts of different ages were also tested on large animal models.

Normal contractile function in its basic form depends on the availability of high-energy phosphates, maintenance of intracellular pH, ion homeostasis, and cell membrane homeostasis, which facilitates aerobic metabolism. Disruption of any of these processes can lead to irreversible damage after myocardial ischemia [15]. In addition, stimulation of anaerobic glycolysis, scavenging of anoxic radicals, and prevention of intracellular calcium accumulation are thought to play an important role in preserving the function during cardiac arrest [15, 16]. Cardioplegia is usually based on metabolic arrest combined with hypothermia to address these problems [17].

The most commonly used method of inducing contractile arrest is the delivery of high concentrations of potassium ions into the extracellular space. Although the advantages of this strategy are its simplicity and rapid onset of cardiac arrest, the speedy washout of the potassium-containing solution and the fact that potassium causes depolarization of cardiomyocytes are major drawbacks of this approach. It was recognized early on that cellular hyperpolarization during ischemia slows not only the rate of energy consumption but also the intracellular accumulation of noxious calcium ions. To achieve this, polarizing agents such as procaine and lidocaine, as well as calcium-competing ions such as magnesium, were added to the solutions. The addition of red blood cells in varying amounts arose from the concept of the need to deliver oxygen and energy during ischemia, although the exact mechanism by which red blood cells help protect the myocardium remains controversial. Numerous cardioplegic solutions and protocols were developed based on these principles [18]. While it is beyond the scope of this article to describe the many variations, the ways in which del Nido cardioplegic solution addresses these issues are described here. It is important to note that although the ingredients were designed and combined taking into account the characteristics of immature myocardium, their use in adult patients with acquired cardiovascular disease has been reported.

PLASMA-LYTE A STOCK SOLUTION

Del Nido cardioplegia contains Plasma-Lyte A stock solution which has an electrolyte composition similar to that of extracellular fluid (Baxter Healthcare Corporation, Deerfield, IL). The electrolyte concentration before adding cardioplegic

additives is 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 manufacturer states a pH of 7.4. The cardioplegia additives to this stock solution are listed in Table 1. This composition serves as the crystalloid component, which is mixed with blood at a ratio of four parts crystalloid to one part fully oxygenated whole blood of the patient (usually obtained from the heart-lung machine circuit). It is important to note that there is no calcium in the stock solution. The final calcium concentration in this cardioplegia can be described as trace, since 20% of the volume of the infused solution contains the patient's blood. This is an important point, since trace calcium concentrations in cardioplegic solutions were shown to be preferable to acalcium or normal levels [15, 19–21].

Table 1

Components of Del Nido solution

Solution component	Volume
Plasma-Lyte A	1 l
Mannitol 20%	16.3 ml
Magnesium Sulfate 50%	4 ml
Sodium Bicarbonate 8.4%	13 ml
Potassium Chloride (2 mEq/ml)	13 ml
Lidocaine 1%	13 ml

MANNITOL

Myocardial injury during cardioplegia and subsequent reperfusion may be due in part to the action of anoxic radicals, including superoxide anion, hydrogen peroxide, and hydroxyl. These radicals are normally enzymatically neutralized within the cell, but this process is suppressed during myocardial arrest [16, 22]. In addition, myocardial edema was also associated with post-ischemic myocardial injury. Hyperosmotic mannitol was shown to scavenge free radicals and reduce myocardial cell edema [23].

MAGNESIUM SULFATE

Myocardial function is closely related to intracellular calcium concentration. Normal myocardial calcium flux increases intracellular calcium for contraction, and decreases it for relaxation. If calcium is allowed to accumulate in the myocardium, relaxation may be interrupted, leading to diastolic stiffness and poor recovery [24]. Magnesium was shown to be a natural calcium channel blocker [25]. It is probably due to this effect that magnesium improves ventricular recovery during hypothermic cardioplegia in combination with low calcium levels [19, 26].

SODIUM BICARBONATE

Aerobic metabolism is usually not possible during the entire period of myocardial arrest. Therefore, it is necessary to maintain anaerobic glycolysis. Anaerobic glycolysis and ATP production were shown to be inhibited by excess hydrogen ion accumulation [17, 27, 28]. Del Nido cardioplegic mixture includes sodium bicarbonate as a buffer solution to remove excess hydrogen ions, and maintain intracellular pH. It is also important to note that red blood cells contain a high concentration of carbonic anhydrase, an enzyme that helps burn hydrogen ions with bicarbonate to form carbon dioxide and water. This property of red blood cells perhaps plays the most significant role in cardioplegia.

POTASSIUM CHLORIDE

Hyperkalemia is the most common method of arrest in cardiac surgery because it provides rapid arrest [29, 30] and reliable recovery, but was shown to have its limitations. It is capable of causing depolarized arrest. Depolarized arrest may be associated with poor myocardial recovery due to intracellular accumulation of sodium and calcium during the arrest period [30]. Lidocaine probably suppresses these negative effects by increasing the period of time during which electromechanical activity is absent. The potassium level in del Nido cardioplegia is 24 mEq/L.

LIDOCAINE

Lidocaine is a sodium channel blocker and is a commonly used antiarrhythmic agent. Sodium channel blockade prolongs the refractory period of the cardiomyocyte [24]. When cardioplegia is performed under ideal conditions, without washout, this effect is prolonged because lidocaine remains in adequate concentrations to continuously act on the myocardium. In addition, sodium channel blockade helps counteract the negative effects of hyperkalemic depolarization arrest by polarizing the cell membrane to some extent, and preventing the accumulation of sodium and calcium inside the cell. Depolarized arrest can lead to sodium and calcium accumulation via metabolic mechanisms, and sodium channel blockade helps prevent this [30]. A 2009 study by O'Brien et al. [31] showed that del Nido cardioplegia reduced calcium accumulation during myocardial ischemia in the setting of depolarized arrest. It should be noted that del Nido cardioplegia can be classified as a modified depolarizing agent, primarily due to the properties of lidocaine and magnesium.

ADDITION OF PATIENT BLOOD

Del Nido cardioplegia is delivered with 20% by volume of fully oxygenated patient blood, which maintains aerobic metabolism for a certain period of time, and provides buffering properties that promote anaerobic glycolysis. Blood in cardioplegia was also shown to improve coronary perfusion during cardioplegia [32]. Moreover, studies have shown that blood cardioplegia preserves myocardial metabolism and function [33], and results in less metabolic ischemic stress and reperfusion injury compared to non-blood cardioplegia in various groups of patients undergoing cardiac surgery, namely in groups with congenital defects [34].

The cardioplegia hematocrit can be calculated by multiplying the hematocrit of the blood component (taken from the heart-lung machine circuit) by the 20% fraction. For example, the del Nido cardioplegia hematocrit would be 6%, if a 20% portion of blood had a hematocrit of 30%.

HYPOTHERMIA

Reducing myocardial metabolic rate by hypothermia is common practice when delivering cardioplegia [24, 29, 35]. Hypothermia reduces the consumption of oxygen and high-energy phosphates, while providing additional cardioplegic effect at low temperatures [5]. In our scheme, del Nido cardioplegia is delivered through a chilled coil. The delivery temperature using this simple method is usually 8-12°C.

CARDIOPLEGIC LOOP

At the University Clinical Hospital No. 1 (Sechenov University, Moscow), we use a recirculation system to deliver cardioplegia. This system does not connect to or draw blood directly from a standard heart-lung machine. “Dead space volume” in our recirculation system is only 1 mL (plus the root cannula volume), and this is an important design consideration. The disposable tubing set we use (Fig. 1) consists of a cardioplegia bag connecting line with an integrated 0.2-μm crystalloid filter, a cardioplegia reservoir, a pump loop, a chilled coil, a temperature control site, a pressure control site, and a bubble trap with an integrated 270-μm filter; all with tubing that connects to sterile lines at the surgical site. We use several different individual tubing sets for our bypass circuits. Each kit contains identical sterile cardioplegia table lines that are connected to a special cardioplegia tubing set during the preparation of the heart-lung machine. Final delivery of the solution is most often accomplished through a 14- or 18-Fr aortic root cannula (Medtronic Inc., Minneapolis, MN). Coronary perfusors are used when necessary. We do not use retrograde administration into the coronary sinus.

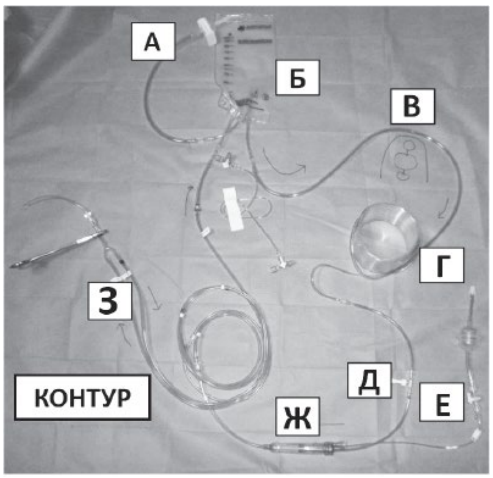

Fig. 1. Lines located on the operating table, connected to the circuit (А). Cardioplegia bag connection line with integrated 0.2-μm crystalloid filter (Б). Cardioplegia reservoir (В). Pump loop (Г). Chilled coil (Д). Temperature control point (Е). Pressure control point (Ж). Bubble trap with built-in 270 μm filter (З)

The volume of the entire cardioplegia circuit (the circuit connected to the cardioplegia tubing set) is 125 ml. We maintain a minimum volume of 25 ml in the cardioplegia reservoir to prevent air trapping. Therefore, for calculations we use a primary volume of 150 ml. Figure 2 shows our individual cardioplegia set in use.

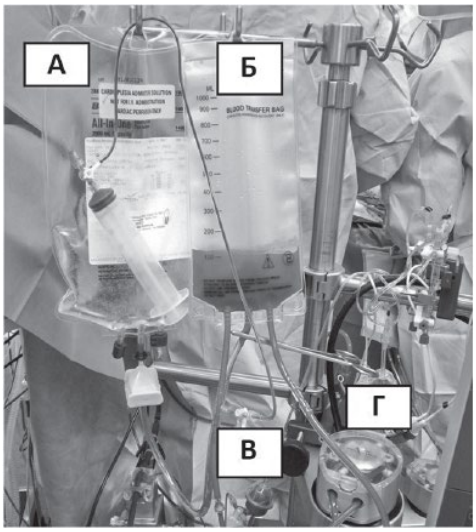

Fig. 2. Circuit together with the cardiopulmonary bypass machine (А). Cardioplegia bag with crystalloid component (Б). Cardioplegia reservoir bag in which components are mixed and recirculated in a ratio of 4:1 (crystalloid:blood) (В). Stopcock, line and syringe used to introduce blood from the bypass circuit into the cardioplegia circuit (Г). Cardioplegia roller pump

DOSAGE

Del Nido cardioplegic solution is usually given as a single dose of 20 ml/kg. The maximum cardiac arrest dose is normally limited to 1 L for patients weighing more than 50 kg. Additional volume of cardioplegia solution may be given for hypertrophied hearts, patients with aortic insufficiency, or those with known coronary disease, depending on the effectiveness of the initial dose and surgeon preference. For procedures requiring myocardial ischemia durations of less than 30 minutes, a lower dose of 10 ml/kg may be used. Subsequent doses are not routinely given except in rare cases of electrical activity or exceptionally long cross-clamp times (>3 hours) at the discretion of the surgeon.

It is important to mix the crystalloid component of the cardioplegia solution with the patient's blood properly to achieve the correct parts ratio of four parts crystalloid to one part patient blood. In a clinical setting, we multiply the patient's weight in kilograms by 20 ml/kg to obtain the total cardioplegia dosage volume. We then add the 150 mL volume of circuit primer and divide the total by 5 to obtain the blood component volume. After that, taking the volume of the delivered dose, adding 25 mL to account for the minimum reservoir level, and subtracting the blood component, we obtain the volume of crystalloid that must be in the cardioplegia reservoir before blood is added. The patient's fully oxygenated blood is withdrawn from the cardiopulmonary bypass circuit after the patient has been connected to the bypass circuit for at least 1–2 minutes. This precise volume is withdrawn from the circuit via a manifold syringe, and then injected into the separate recirculating cardioplegia solution delivery system. As a result, only the 20 ml/kg cardioplegia dosage plus the minimum reservoir volume of 25 ml are in the cardioplegia reservoir recirculation bag awaiting delivery. Table 2 provides examples of calculations. It should be noted that additional doses only require the perfusionist to calculate the needed amount of blood and crystalloids to be directed into the delivery reservoir, since circuit priming is already taken into account.

Table 2

Calculation of the cardioplegia dosage for a patient weighing 70 kg

Calculation of the cardioplegia dosage for a patient weighing 70 kg
— 70 kg × 20 ml/kg = 1400 ml cardioplegia dosage volume
— 1400 ml dosage volume + 150 ml primer volume = 1550 ml total system volume
— 1550 ml total system volume/5 = 310 ml blood component volume
— (1400 ml dose volume + 25 ml minimum reservoir volume) - (310 ml blood component volume) = 1115 ml crystalloid cardioplegia volume in the reservoir before adding blood, which will give the correct mixture ratio (3.6:1) for this 70 kg patient
— The perfusionist will obtain the required dosage and mixture volume for this patient by recirculating 1115 mL in the cardioplegia reservoir before bypass, and then adding 310 mL of the patient's whole blood after bypass. After administering a 1400 mL dosage of cardioplegia, the perfusionist will be left with a minimum working level of 25 mL in the cardioplegia reservoir

CARDIOPLEGIA DELIVERY

Delivery is initiated with the surgeon moving the clamp on the table lines from the outlet to the return limb. The flow is controlled by the perfusionist on the heart-lung machine. We typically deliver a 20 mL/kg cardioplegia dose over 1–2 minutes at a system pressure of 100–200 mmHg. We do not monitor aortic root pressure, although the surgeon carefully monitors aortic root distension during delivery to prevent capillary damage due to high shear forces when delivered too rapidly. In other words, it is quite simple from a clinical perspective to estimate the initial delivery rate by taking half the delayed dosage volume and using it as the flow rate. For example, in a 12 kg patient the dosage volume would be 240 ml (20 ml/kg cardioplegia x 12 kg). An initial infusion rate of half this (120 ml/min) would be a reasonable estimate to achieve an infusion rate of 1–2 minutes at a system pressure of 100–200 mmHg, at least when using our individual cardioplegia regimen.

Initial flow rates for aortic root insertion are limited to 300 mL/min in larger patients. The initial flow rate when inserted into the coronary ostium can be classified as "barely on." The cardioplegia flow for all techniques is adjusted from the initial flow based on the surgeon's observation of cardiac status and electrical activity. Cardioplegia system pressures can be higher by increasing flow, using smaller radicular needles, and inserting selectively into the orifice. This higher system pressure is not linearly related to root pressure, but the surgeon must still visually monitor delivery.

The del Nido cardioplegia solution was originally developed for infants and young patients but is gradually finding its way into adult cardiac surgery. This method of cardioplegia consists of the solution being administered typically as a single dose of 20 ml/kg antegradely at 8–12°C through a recirculating delivery system. The unique composition reduces energy expenditure, blocks calcium influx into the intracellular environment, removes hydrogen ions, preserves high-energy phosphates, and initiates anaerobic glycolysis during myocardial arrest. O'Blenes et al. [21] demonstrated experimentally on a rat aged heart model that del Nido cardioplegia resulted in lower intracellular calcium levels and more frequent spontaneous contractions. The same center also showed a lower troponin T release in pediatric patients compared with the cardioplegia strategy in adults [31]. More recently, Charette et al. [36] published a retrospective study of patients with congenital heart disease who had myocardial ischemia duration greater than 90 minutes. This study found no significant difference in postoperative complications with the use of del Nido cardioplegia compared with the previous multidose cardioplegia strategy at this institution.

CONCLUSION

In the last decade, the use of del Nido cardioplegia has spread to adult cardiac centers due to reports of its success. However, there are no prospective randomized controlled trials of this cardioplegia strategy versus other methods to compare the results with.

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