Editorial

# New insights on the use of del Nido cardioplegia in the adult cardiac surgery

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The use of cardioplegia solution represents the most important strategy to protect myocardial muscle during cardiac surgery (1). Cold crystalloid cardioplegia associated with mild-to-moderate hypothermia has the advantage to decrease the oxygen consumption, offers some degree of myocardial protection during period of low flow or low perfusion pressure.

Blood was then found to be an important vehicle for delivery of potassium in the cardioplegic solution, either with moderate hypothermia than at physiological temperature. Warm blood cardioplegia has been proposed as a safe technique for myocardial protection based on the rationale that blood, as opposed to crystalloid solution, could potentially improve postoperative cardiac outcomes, because it more closely approximates the normal physiology, i.e., carrying oxygen to the myocardium or ensuring a less hemodilution.

Several studies published in the 80s and 90s have not showed substantial differences between type (crystalloid versus blood), temperature of solution (cold, tepid, or warm), or via administration (antegrade versus retrograde) of the cardioplegia, and therefore, it is still debated which type of cardioplegia is better for myocardial protection during cardiac arrest (2-6). The more recently introduced del Nido cardioplegic solution (7,8) has the rationale to preserve the intracellular phosphates concentration, the intracellular pH value, and to reduce the intracellular damage by the calcium ion influx during ischemic arrest, especially during surgical procedures requiring long time, i.e., for the treatment of congenital heart disease. The del Nido cardioplegia is delivered with 20% by volume fully oxygenated patient blood, which supports aerobic metabolism for a finite period of time and provides buffering properties to promote anaerobic glycolysis. Del Nido cardioplegia was mainly developed for use in the pediatric population to address the inability of immature myocardium to tolerate high levels of intracellular calcium following cardiac surgery (9,10). The main differences in the del Nido solution in comparison with other types of cardioplegia are given by the presence of concentration of mannitol, magnesium sulphate and, in particular, lidocaine. Ad and colleagues performed an interesting multicentre randomized trial, involving six American cardiovascular and thoracic centers, aimed to evaluate if the use of del Nido cardioplegia in comparison with blood-based cardioplegia is safe and effective also in adult cardiac surgery (11).

They included 89 stable patients who underwent isolated coronary artery bypass grafting (CABG) surgery, isolated single valve surgery, and concomitant CABG and single valve surgery. Forty-eight patients were randomized to receive del Nido cardioplegia (del Nido group), 41 whole blood cardioplegia (control group). Primary end-points included myocardial preservation by return to spontaneous rhythm, defibrillation requirement, need for inotropes use, and troponin release at 4 time points: baseline at anaesthesia induction, 2 hours after cardiopulmonary bypass weaning, 12 and 24 hours after admission in intensive care unit, respectively. Preoperative and intraoperative characteristics were similar in both groups. Patients enrolled in the del Nido group received 1 L of the del Nido cardioplegic solution after aortic cross-clamp, with an additional 500 mL in presence of left ventricular hypertrophy, at a temperature

of 6–10 ℃; The dose of whole blood cardioplegia was 1–2 L, with subsequent doses administered every 20 minutes, at a temperature of 8–11 ℃.

As compared with control group, the del Nido group had a greater number of patients who retuned in spontaneous rhythm (97.7% *vs.* 81.6%), a lower number of defibrillations after coronary reperfusion (4.7% *vs.* 13.2%), and fewer patients required inotropic support (65.1% *vs.* 84.2%), although these differences did not reach a statistical significance, at a level of P value greater than 0.001. Aortic cross-clamp time was shorter for del Nido group (70 *vs.* 83 minutes, P=0.018). Troponin I release was similar in both groups, although a lower release was observed in the del Nido group at 12 and 24 hours after operation in comparison with the control group (P=0.040).

On the contrary, as expected, the mean total volume of cardioplegia (1,746±852 *vs.* 5,077±2,457 mL) and the number of cardioplegia's doses per patient was higher in the control group (P<0.001, for both comparisons). The incidence of morbidity was low, with no stroke, perioperative myocardial infarction, renal failure, operative mortality. In light of these results, Ad and coworkers concluded that del Nido cardioplegia appears to be non-inferior to the conventional strategy of myocardial protection in the setting of adult cardiac surgery, and that it can be used safely, leading to comparable clinical outcomes. Similar results were observed in two studies published by Li (12), and by Mishra (13) and coworkers. In the first study, in a meta-analysis comparing del Nido cardioplegia with conventional cardioplegia in adult cardiac surgery, Li reported cardiopulmonary bypass and cross-clamp times significantly shorter with the use of the del Nido cardioplegia, but no difference in myocardial enzyme release, postoperative inotropic support, atrial fibrillation and in-hospital mortality was found between the two groups (12). In the second study, as compared with St. Thomas' cardioplegic solution, the del Nido solution leaded to shorter cardiopulmonary and aortic cross-clamp times, reduced cardioplegia doses, with a safety clinical profile comparable to St. Thomas' solution (13).

Over the past decades, the question of which solution, temperature or mode of administration of different types of cardioplegia provides a better myocardial protection during cardiac surgery has been widely discussed. Experimental studies have suggested a more favorable outcome with the use of blood cardioplegia in comparison with cold crystalloid cardioplegia. Several clinical studies with or without randomization have been performed to assess which cardioplegic solution guarantees a better myocardial protection, but some studies have reported a favorable outcome of the blood (cold or warm) cardioplegia (2-5,14,15), others have not been able to demonstrate any difference (16-18). In another study a worse outcome for patients receiving cold blood cardioplegia has been reported (19). Finally, two studies on the del Nido solution failed to show significant difference in serum troponin levels (20,21).

This debate perfectly includes the findings observed by Ad and coworkers, showing potential benefit of del Nido solution that has the advantage in requiring shorter aortic cross-clamp and cardiopulmonary bypass times in comparison with other types of cardioplegia intermittently administered.

In our institution we performed a retrospective, not randomized, study on the use of warm blood cardioplegia or cold crystalloid cardioplegia antegrade intermittently administered in one hundred and ninety-one stable patients undergoing aortic valve replacement with or without CABG. Serum levels of total CK (U/L), CK-MB (ng/mL), and cardiac troponin I (ng/mL) were lower in the crystalloid cardioplegia group of patients in comparison with warm blood cardioplegia group, in particular, at the time of the admission in intensive care unit. The CK-MB/CK ratio >10% (5.9% *vs.* 7.8% of the patients; P<0.0001), was lower in the cold crystalloid cardioplegia group. We concluded that a significant decrease of myocardial enzyme release can be observed with the use of cold crystalloid cardioplegia, but this difference did not translate into clinical outcomes, that were found similar in both types of cardioplegia. This made us hypothesize that in presence of left ventricular hypertrophy, i.e., in presence of aortic valve disease, a better myocardial protection can be achieved with the use of a cold rather than a warm cardioplegia (22).

An important aspect highlighted by Ad and colleagues is the potential benefit of del Nido solution in preventing ventricular arrhythmias during coronary reperfusion after aortic clamp removal, thanks to the effect that lidocaine has in better preserving the intracellular pH, in limiting the intracellular entry of calcium ion, and to promote the release of nitric oxide. In fact, in their study they report a lower incidence of defibrillation after aortic clamp removal (4.7% *vs.* 13.2%) compared to the control group (11). In their study, however, this difference did not translate into a different clinical outcome, also because the study was conducted on patients with a normal systolic function of the left ventricle. It can be hypothesized that in patients with systolic left ventricular dysfunction or marked cardiac

 

dilatation, a more rapid recovery of the cardiac rhythm after aortic de-clamping, may reduce the risk of myocardial damage and therefore, the risk of postoperative low cardiac output syndrome.

In conclusion, we congratulate the authors on the methodology approached in the study and on the obtained in-hospital results, and also on the clarity with which the data of the randomized trial in question were presented.

From the data obtained in this study, due to the small sample size, we cannot try any definitive conclusion about what is the best method of myocardial protection during adult cardiac surgery. The clinical bottom line of the study is that del Nido cardioplegia can be used safely also in adult cardiac surgery, as well as for the treatment of congenital heart disease, in the ambit of the different types of cardioplegia that are currently available.

To test del Nido cardioplegia effectiveness on myocardial protection more broadly, studies that include larger patient samples and interventions requiring very long aortic clamping times are necessarily warranted.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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