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Review

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Del Nido cardioplegia: from an infant conceive to an adult life - a brief review of the current evidence in adult patients

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Abstract

The increasing number of minimally invasive procedures prompted the quest for a simple and effective single shot cardioplegia to allow the surgeons to focus on their workflow. The originally pediatric Del Nido solution was successfully tested in several centers and gradually extended to regular coronary and valvular cases. In the present review we report the current evidence on the use of the Del Nido solution in adult patients.

Keywords: Del Nido cardioplegia, adult cardioplegia, myocardial protection, blood cardioplegia, single shot cardioplegia

INTRODUCTION

Adult cardiac surgery has changed in the last decade. In the 2018 the STS[1] database reports that about 75% of the patients submitted to myocardial revascularization had 3 or more grafts with an increasing number of non-elective procedures, diabetic and heart failure patients. At the same time 23% of the all the isolated mitral procedures performed in 2016 were minimally invasive and the isolated aortic valve procedures, the second most common cardiac operation, undergoing key-hole surgery have a steady increase. Clearly we are facing more complex procedures and worse clinical characteristics of our patients. This can imply longer cross clamp times which is a well-known risk factor in cardiac surgery. On the other hand the available cardioplegic solutions to protect the heart need to be repeated every 10 to 20 min or continuously infused in a retrograde fashion through the coronary sinus. Although the results with the current cardioplegias are consistently good, some surgeons, in particular those who have focused in minimally invasive procedures, are searching for a "*solution*" which could combine effective and consistent long lasting myocardial protection with easy of deliver.

In the last few years, when its original the patent expired, the paediatric del Nido cardioplegia (DNC) has been increasingly used in adult patients[2]. This cardioplegia allows for an interval between infusions up to 90 min and has some unique features that appear to be promising to the adult cardiac surgeons.

The DNC is a 1:4 blood cardioplegia which can be classified as a modified depolarizing cardioplegia, containing Lidocaine and Magnesium. Clinically it has been validated in valve surgery[3] and at the moment, in low risk coronary patients[4]. We hereby are summarizing the basic concepts behind its formulation and use, along with the available evidence in the adult patients.

DEVELOPMENT OF DNC

For long time paediatric cardiac surgeons had to rely on the common adult cardioplegic solutions to operate on their patients. However, the crystalloid solutions in use in the 80's and early 90's had controversial results in young populations with, for instance, the St Thomas solution being reported either effective[5] or ineffective[6]. Although infant and paediatric hearts have some distinctive histologic and metabolic features, a "dedicated" cardioplegia was missing. Histologically the paediatric heart has a poorly developed sarcoplasmatic reticulum[7], fewer mitochondria, a higher concentration of poly unsaturated fatty acids[8] in the cell membrane and a deficient free radical scavenge system with less active superoxide dismutase, catalase and glutathione reductase[9]. In addition these hearts depends more on the extracellular calcium for contraction. At Pittsburgh University Hospital the team led by Pedro J. del Nido focused on many of these aspects and developed a solution preventing the intracellular accumulation of Calcium, providing effective free radicals scavenge whit maintenance of the anaerobic glycolysis and assuring effective buffering during prolonged periods of cardiac arrest. A detailed description of the development of the cardioplegia is available in the literature[10].

COMPONENTS

The DNC is a 1:4 Blood to Crystalloid solution with additional components to achieve depolarized arrest and mitigate the effects of temporary myocardial ischemia [Table 1].

Plasmalyte a solution

The Plasma Lyte A (Baxter Health Care Corp. Deerfield, IL USA) solution forms the crystalloid base of the DNC. It is an extracellular (Na^+ 140 mEq, K^+ 5 mEq/L) solution with a final pH of 7.4 and an osmolarity of 294 mOsm/L. It is commonly used as a fluid volume replacement infusion in many clinical conditions. Noticeably it does not contain glucose.

Potassium

Similarly to other common depolarizing solutions, the final content of K^+ ions in the DNC is about 24 mEq/L which is obtained from the basal content of Plasma-Lyte (5 mEq) plus the added 26 mEq and an assumed 4.5 mEq/L from the patient's blood.

Table 1. Composition of the del Nido cardioplegia

Del Nido formulation	Plasma-Lyte a solution 1000 mL
Plasma Lyte A Solution 1 L	Sodium 140 mEq
Mannitol 20 % (16.3 mL)	Potassium 5 mEq
Magnesium Sulfate 50% (4 mL)	Magnesium 3 mEq
Sodium Bicarbonate 8.4% (13 mL)	Cloride 98 mEq
Potassium Cloride 2 mEq/L (13 mL)	Gluconate 23 mEq
Lidocaine 1% (13 mL)	Acetate 27 mEq
Blood : Crystalloid 1:4	

As known Potassium increases the resting potential of myocytes to about -46 mV, well above the depolarization threshold of – 65 mV. In doing so it leaves the cells in a state of arrest. Hence, indirectly potassium blocks the inward current of Na^+ during the phase 0 of the myocardial action potential

Lidocaine

Lidocaine is a class I antiarrhythmic drug that directly blocks the Na^+ channels in phase 0. Its half-life is relatively long and is obviously increased by the absence of coronary circulation. It also blocks the so called "window" channels which remain open during the depolarized arrest and allow some Na^+ and Ca^{2+} inward current in the cell. Lidocaine therefore allows for prolonged periods of cardiac arrest and participates in the control of intracellular accumulation of calcium during the ischemic period.

Magnesium

Magnesium is a natural Calcium channels blocker. Contrary to the skeletal muscle, the cardiac myocyte is largely dependent from extracellular calcium for its contraction. Calcium ions enter the cardiac myocyte during phase 2 plateau of the action potential through L-Type channels which are blocked by Magnesium ions. In doing so Magnesium prevents the contraction of the myocytes and accumulation of Calcium in the cell. Interestingly both paediatric and "aged" cardiomyocytes have an altered homeostasis of Calcium which can be modulated by Magnesium

Mannitol

Mannitol is a common additive to cardioplegia solutions. Its usage prevents cellular oedema and scavenges free radicals. The cell membrane of immature myocardium has high concentration of poly unsaturated fatty acids providing more sites for oxidative damage, on the other hand oxidative stress is believed to be potent promoter of myocardial aging.

1:4 Blood ratio

The addition of blood to crystalloid cardioplegia is far beyond the simple concept of substrates and oxygen deliver to the arrested heart. As the haemoglobin dissociation curves are altered during hypothermia, the oxygen deliver is minimal and dependent from the gas dissolved in the solution. However, blood proteins and the other components have several potential benefits which include buffering from proteins and carbonic anhydrase contained in red cells, free radicals scavenge and more favourable rheological properties. In addition, as a result of the lower haematocrit compared to the classic solution with a 4:1 ratio, the DNC has a very low Calcium content which enhances the effects of Lidocaine and Magnesium.

DELIVER AND TECHNICAL ASPECTS

With the widespread use of blood cardioplegias the perfusionist can easily arrange a circuit to deliver the DNC basic crystalloids components in a 4:1 ration with the patient's derived oxygenated blood (> 150 mmH pO_2). Sample circuits drawings are available in the literature from the original Boston Children Hospital and the Cleaveland Clinic[11]. Table 1 depicts the current setting in use in our Centre. The DNC is usually

Table 2. Literature summary

Reference	Population (*n*)	Study design	Significant results in DNC group	No differences
Yerebakan *et al*.[24]	Acute MI CABG DNC = 48 WCBC = 40	Retrospective	↓ CPB ↓ X- Clamp	Enzyme relese EF% Postperative support Mortality
Sorabella *et al*.[18]	Reoperative AVR DNC = 52 Blood = 61	DNC *vs.* blood Retrospective	↓Cardioplegia volume	CPB, X-clamp time Complication rate
Mick *et al*.[3]	Isolated Valve Aortic = 85/85 Mitral = 110/110	Retrospective 1:1 Propensity score Matched	Aortic ↓ CPB, ↓ XC lamp, ↓Glucose ↓ Insuline Mitral ↓ Insuline ↓ Glucose	Ensyme Release EF% Clinical results
Ota *et al*.[17]	AVR (240) DNC = 178 Blood = 62	DNC *vs.* blood Retrospective Propensity matched 54 pairs	↓CPB, ↓ X-clamp ↓Use of retrograde	Inotropic support
Mishra *et al*.[31]	CABG or double valve DNC = 50 Blood = 50	DNC *vs.* blood Retrospective	↓CPB, ↓ X-clamp ↓Redosing ↓Ejection fraction	Complication rates
Timek *et al*.[23]	CABG DNC = 82 CB = 82	DNC *vs.* CB Rterospective Propensity score matched pairs	↓ Glucose	Cross Clamp Inotropes Enzyme Release EF%
Guajardo *et al*.[4]	CABG (408) DNC = 159 Blood = 249	DNC *vs.* blood Retrospective	↓ Need defibrillation ↓Transfusion ($P < 0.08$)	CPB, X-clamp time Length of stay Mortality
Vistarini *et al*.[27]	Min. invasive AVR DNC = 25 Blood = 21	DNC *vs.* blood Retrospective	↓ Need defibrillation ↓CK-MB ↓Insulin use	Complication rate Mortality
Kim *et al*.[21]	Valve DNC = 149 Blood = 892	DNC *vs.* blood Retrospective Propensity matched 111 pairs	↓CPB, X-clamp ↓Troponin ↓Transfusion	Inotropic support Mortality Complication rates
Hamad *et al*.[28]	AVR/CABG DNC = 25 Blood = 25	DNC *vs.* blood Retrospective	↓CK-MB, troponin T ↓CPB, X-clamp	Inotropic support Operative time Length of stay Complication rates
Ziazadeh *et al*.[29]	Min invasive AVR DNC = 77 Blood = 101	DNC *vs.* blood Retrospective Propensity matched 63 pairs	↓CPB, X-clamp ↓Glucose levels	Troponin T Ejection fraction Complication rates
Koeckert *et al*.[30]	Min. invasive AVR DNC = 59 Blood = 122	DNC *vs.* blood Retrospective Propensity matched 59 pairs	↓Redosing ↓Cardioplegia volume ↓Use of retrograde	CPB, X-clamp time Inotropic support Transfusion Length of stay Complication rates
Ad *et al*.[26]	CABG ± valve DNC = 48 Blood = 41	Randomized, controlled	↓ A.Fib Postop (*) ↓ Troponine (*)	CPB, X-clamp time Complication rates Inotropic support Need defibrillation
UCAK *et al*.[25]	CABG elective DNC = 112 IWBC =185	DNC *vs.* IWBC Randomized Controlled	↓ CPB ↓ X-clamp ↓ Glucose	Enzyme release Clinical events
O'Donnel *et al*.[20]	CABG DNC=54 BC = 27	DNC *vs.* BC Retrospective	↓ CPB ↓ X-clamp ↓ Defibrillations	No difference in clinical outcomes
Pragliola *et al*.[33]	All kinds of adult surgery including emergencies DNC =102 IWBC = 102	DNC *vs.* IWBC Retrospective Propensity score matched pairs	↓Ejection fraction in low EF subgroup	No differences overall

AVR: aortic valve replacement; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass time; DNC: del Nido cardioplegia; X-clamp: cross-clamp time; IWBC Intermittent warm blood cardioplegia CC Cold Cardioplegia BC Blood Cardioplegia. *(see text for details) Note that alpha value for statistical significance was $P < 0.001$, thus nonsignificant trends exist.

delivered in the aortic root at a dose of 20 mL/kg with a maximum dose of 1000 mL. Rate of infusion is usually between 150 mL/min to 300 mL/min for a pressure of 100 mmHg in 2 to 4 minutes. The cardioplegia's circuits include a heat exchanger to deliver the solution at 4 °C for a final myocardial temperature of less of 15 °C. As known the myocardium Oxygen consumption decreases of 50% for any 10 °C reduction of temperature, at 10 °C the oxygen requirements should be in the 15% to 20% range of the baseline. Hence ice slush for local temperature control is added by the surgeon in the pericardium at the aortic cross clamp time. However, continuous myocardial temperature is not routinely used.

The cardioplegia can also be infused directly into the coronary arteries in case of severe Aortic regurgitation, as can be infused retrogradely at the some doses used in the aortic root although this is not common practice according to the literature. Unlikely other blood cardioplegias, we strongly advise not to use a continuous infusion. This can result either in an excess of volume or Lidocaine and magnesium. Najjar *et al*.[12] in a series of 14 patients undergoing re-operative surgery and continuous infusion reported a mean total volume of 4367 mL ± 751 mL for an aortic cross clamp time of 81 min ± 35 min. With retrograde continuous infusion in patients submitted to aortic valve reimplantation, Jiang *et al*.[13] reported a 26% incidence of postoperative heart block resulting in 6.7% incidence of permanent heart block. Due to the limited number of patients and the inherent surgery they were submitted to, it is not possible to reach a definite conclusion, but caution is advised.

EXPERIMENTAL STUDIES

The conflicting evidences on the premature myocardium metabolism which were evident at the time the DNC was developed at Boston Children Hospital have been stressed by Matte in his report. In brief the Del Nido was conceived as a hyperpolarizing (K^+), extracellular (Na^+) glucose free (Plasmalyte), hyperosmolar (Mannitol), buffered (Bicarbonate, blood proteins) solution controlling the calcium influx into the cells (Magnesium and Lidocaine). The presence of lidocaine in an unperfused coronary bed (slowly wiped off by the collateral coronary flow) allows for long intervals between the infusion of the solution. This is as important as the maintenance of a low myocardial temperature and the use of the cold cardioplegic solution when manually testing the anastomosis during CABG surgery. These details are collateral, but not less important parts of the technique in adults[14].

However, there are at least two experimental studies supporting the use of the DNC in aged hearts. During cardioplegic arrest induced by DNC in an isolated cells model from senescent rats, the intracellular Calcium content was lower and the cells were not reactive to electric filed stimulation as well as they did not develop hypercontraction at reperfusion contrary to the same model treated with conventional cardioplegias. The Authors concluded that according to these results, the DNC had the potential to better protect senescent hearts preventing electromechanical activity during the arrest and hypercontraction at the time of reperfusion[15]. Similarly, in an isolated working model of senescent hearts, the treatment group that underwent 60 min of cardiac arrest induced by DNC had better contractility and lower enzyme release compared to the group treated with conventional cardioplegia[16].

EXPERIENCES IN ADULT PATIENTS

Interestingly, although it is now clear that major cardiothoracic units are regularly using the DNC solution, available studies deal only with limited subpopulations.

Matte *et al*.[10], describing the development of the DNC reports the regular use in Adult Congenital cases at Boston Children Hospital. Ota *et al*.[17] and Sorabella *et al*.[18] published their experiences with first time and re-operative Aortic Valve surgery, all with safe and comparable results. Mongero[19] state that the DN cardioplegia is the only solution in use in their Centre, the Columbia University Presbiterian Hospital NY, since 2011 and call for a broader use of it in adults. O'Donnell *et al*.[20] reports that the DNC is the cardioplegia of choice in CABG since 2015.

In many institutions, including ours, the del Nido was initially used in minimally invasive Mitral cases and then gradually extended to cover all procedures. This path, though not openly stated, was probably started at the Columbia University and followed in Cleaveland[21] where the Del Nido was propensity matched with good results to the Buckberg solution in minimally invasive or robotic valvular cases and showed better glucose control, reduced cross-clamp and operative times.

As the field of minimally invasive and robotic surgery is rapidly expanding, teams dealing with these techniques are looking for a simple and effective cardioplegia. Amongst the available alternative solutions, the Buckeberg[19] entails a staged deliver in different phases and shorter intervals of ischemia (15 m to 20 m) which can slow down the surgical workflow. Besides, the retrograde infusion in minimally invasive surgery is a sophisticated and sometime difficult technique to control in a limited surgical field. The Custodiol®[22] solution for long time has been the only single shot cardioplegia. Initially introduced for the donor hearts that usually are exposed to long ischemic times during organ procurements, it achieves a long-lasting myocardial protection. However, this solution requires the infusion of a large volume of hyponatremic crystalloid which is usually drained during the donor heart harvest but can be problematic in patients operated with a minimally invasive approach. Although ultrafiltration can help solve this problem, the volume overload and the hyponatremia can complicate the postoperative period.

There are also several studies testing the DNC in coronary revascularization. Timek *et al.*[23] reported on a group of CABG patients receiving the DNC, propensity score matched to a population operated with usual Cold Blood Cardioplegia infused at 15-20 min intervals. Not surprisingly the DNC resulted in a lower volume infused and a lower peak glucose level during cardiopulmonary bypass compared to the matched population. No clinical differences were noted in the outcomes.

The DNC has also been tested in high risk coronary cases with Acute Myocardial infarction by Yerebakan *et al.*[24] in 2014 with excellent clinical results. Two recently published Randomized Controlled Trials (RCT) compared the use of the DNC to the intermittent whole blood cardioplegia in CABG or CABG plus valve surgery. Ucak *et al.*[25] could observe shorter aortic cross-clamp and CPBP times and better glucose control in the DNC group, without meaningful clinical differences in a population with an average Euroscore of 4.1. Similarly, Ad *et al.*[26] conducted the single registered RCT (NCT02442050) for the DNC in adults. The randomized patients had an average STS score of 1.3. Initially designed as a non-inferiority study to include 500 patients, it was prematurely interrupted because the DNC patients had a better rhythm recovery after surgery. The study was then turned into a superiority study with a required level of evidence of $P < 0.001$. With these new parameters there were no clinical differences in the outcome although the peak T troponin level was lesser in the DNC group at $P < 0.04$ without sufficient power to achieve statistical differences. Table 1 summarizes the available studies. Many of them where also included in an extensive metanalysis which favoured the del Nido in reducing the volume of cardioplegia infused, shortening the cardio-pulmonary bypass and cross clamp times and hade comparable results in terms of troponine and CKmb release. All the studies had comparable clinical results[27,32].

In the available literature, the common criticisms to the use of the DNC in adults are two: the limited number of patients included in the studies, usually with a single pathology and the low risk of these groups of patients.

In his elegant statistical study, Kim *et al.*[21] matched two similar groups of 104 patients treated with the DNC or Blood Cardioplegia out of 1041 consecutive patients. Again the DNC showed an advantage in the postoperative peak troponin release and shorter cross-clamp times. Noticeably all kind of procedures were done in these groups, including multiple complex valves and aortic arch surgery. However, the logistic Euroscore II for the DNC group was 2.9 ± 3.3.

Comments and Conclusion

Understandably Lazar[14] put forward a few questions about the use of the DNC in high-risk cases with low EF%, high Euroscore or high Pulmonary Artery Pressures; adult patients in whom the solution has not been extensively tested.

We do not have a definite answer to these questions. In our Centre the DNC quickly took over the IWBC to be the standard solution in use[33]. Over the last 1000 consecutive cases in 2017-2018 we could propensity score match 102 pairs including two groups with a high Euroscore II (mean ESII 10) and one with low EF (EF 30%) in whom the DNC provided sufficient protection without major differences with the IWBC and allowed the surgeon to focus on the his surgical workflow (data in press). There are not clear guidelines on cardioplegic solutions and the debate whether it should be warm or cold, blood or asanguineous, antegrade or retrograde, intermittent, single shot or continuous flooded the surgical literature. Clearly the perfect myocardial protection is the result of a complex interaction of the surgical team with the procedure performed, the patient characteristics, the cardioplegic solution and the technique of delivery. This is coming from practice, consistence and excellence as certainly occurred in all the centres where the DNC was adopted routinely in adult cases.

A large randomized superiority trial enrolling only high risk cases will be difficult to complete and poses several potential problems : some ethical and some very practical. To date, as a result, there are not similar trials registered in the Clinical Trials website.

In conclusion, there is sufficient evidence to engage with the single shot DNC in all the routine cases either valvular or coronary, especially in minimally invasive procedures. Whether this will expand into the moderate and high risk cases will depend from the surgical team preferences.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study: Pragliola C, Hassan E
Performed data analysis and interpretation: Pragliola C, Hassan E, Al Gharni KD
Performed data acquisition, as well as provided administrative, technical, and material support: Alfonso JJT, Al Hossan A, Al Otaibi K, Al Khalaf A.

Availability of data and materials

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Conflicts of interest

All authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Jacobs JP, Badhwar V, Mayer JE Jr, Shahian DM, D'Agostino RS, et al. The society of thoracic surgeons national database 2018 annual report. Ann Thorac Surg 2018;106:1603-11.
2. Spellman J: In Favor of More Generalized Use of del Nido cardioplegia in Adult Patients Undergoing Cardiac Surgery. J Cardiothorac Vasc Anesth 2019;6:1785-90.
3. Mick SL, Robich MP, Houghtaling PL, Gillinov AM, Soltesz EG, et al. Del nido versus Buckberg cardioplegia in adult isolated valve surgery. J Thorac Cardiovasc Surg 2015;149:626-634; discussion 634-6.
4. Guajardo Salinas G.E, Nutt R, Rodriguez-Araujo G. Del Nido cardioplegia in low risk adults undergoing first time coronary artery bypass surgery. Perfusion 2017;32:68-73.
5. Magovern JA, Pae WE Jr, Waldhausen JA. Protection of the immature myocardium. An experimental evaluation of topical cooling, single-dose, and multiple-doseadministration of St. Thomas' Hospital cardioplegic solution. J Thorac Cardiovasc Surg 1988;96:408-13.
6. Wittnich C, Peniston C, Ianuzzo D, Abel JG, Salerno TA. Relative vulnerability of neonatal and adult hearts to ischemic injury. Circulation 1987;76:V156-60.
7. Boland R, Martonosi A, Tillack TW. Developmental changes in the composition and function of sarcoplasmic reticulum. J Biol Chem 1974;249:612-23.
8. Friedman WF. The intrinsic physiologic properties of the developing heart. Prog Cardiovasc Dis 1972;15:87-111.
9. Teoh KH, Mickle DA, Weisel RD, Li RK, Tumiati LC, et al. Effect of oxygen tension and cardiovascular operations on the myocardial antioxidant enzyme activities in patients with tetralogy of Fallot and aorta-coronary bypass. J Thorac Cardiovasc Surg 1992;104:159-64.
10. Matte GS, del Nido PJ. History and use of del Nido cardioplegia solution at boston children's hospital. J Extra Corpor Technol 2012;44:98-103.
11. Kim K, Ball C, Grady P, Mick S. Use of del Nido cardioplegia for adult cardiacsurgery at the cleveland clinic: perfusion implications. J Extra Corpor Technol 2014;46:317-23.
12. Najjar M, George I, Akashi H, Nishimura T, Yerebakan H, et al. Feasibility and safety of continuous retrograde administration of del Nido cardioplegia: a case series. J Cardiothorac Surg 2015;10:176.
13. Jiang X, Gu T, Shi E, Wang C, Xiu Z, et al. Antegrade versus continuous retrograde del Nido cardioplegia in the david i operation. Heart Lung Circ 2018;27:497-502.
14. Lazar HL. Del Nido cardioplegia: Passing fad or here to stay? J Thorac Cardiovasc Surg 2018;155:1009-10.
15. Govindapillai A, Hua R, Rose R, Friesen CH, O'Blenes SB. Protecting the aged heart during cardiac surgery: use of del Nido cardioplegia provides superior functional recovery in isolated hearts. J Thorac Cardiovasc Surg 2013;146:940-8.
16. O'Blenes SB, Friesen CH, Ali A, Howlett S. Protecting the aged heart during cardiac surgery: the potential benefits of del Nido cardioplegia. J Thorac Cardiovasc Surg 2011;141:762-70.
17. Ota T, Yerebakan H, Neely RC, Mongero L, George I, et al. Short-term outcomes in adult cardiac surgery in the use of del Nido cardioplegia solution. Perfusion 2016;31:27-33.
18. Sorabella RA, Akashi H, Yerebakan H, Najjar M, Mannan A, et al. Myocardial protection using del Nido cardioplegia solution in adult reoperative aortic valve surgery. J Card Surg 2014;29:445-9.
19. Mongero LB. Del Nido cardioplegia-not just kids stuff. J Extra Corpor Technol 2016;48:25-8.
20. O'Donnell C, Wang H, Tran P, Miller S, Shuttleworth P, et al. Utilization of del Nido cardioplegia in adult coronary artery bypass grafting-a retrospective analysis. Circ J 2019;83:342-6.
21. Kim WK, Kim HR, Kim JB, Jung SH, Choo SJ, et al. Del Nido cardioplegia in adult cardiac surgery: beyond single-valve surgery. Interact Cardiovasc Thorac Surg 2018;27:81-7.
22. Singh SAS, De SD, Spadaccio C, Berry C, Al-Attar N. An overview of different methods of myocardial protection currently employed peri-transplantation. Vessel Plus 2017;1:213-9.
23. Timek T, Willekes C, Hulme O, Himelhoch B, Nadeau D, et al. Propensity matched analysis of del Nido cardioplegia in adult coronary artery bypass grafting: initial experience with 100 consecutive patients. Ann Thorac Surg 2016;101:2237-41.
24. Yerebakan H, Sorabella RA, Najjar M, Castillero E, Mongero L, et al. Del Nido cardioplegia can be safely administered in high-risk coronary artery bypass grafting surgery after acute myocardial infarction: a propensity matched comparison. J Cardiothorac Surg 2014;9:141.
25. Ucak HA, Uncu H. Comparison of del nido and intermittent warm blood cardioplegia in coronary artery bypass grafting surgery. Ann Thorac Cardiovasc Surg 2019;25:39-45.
26. Ad N, Holmes SD, Massimiano PS, Rongione AJ, Fornaresio LM, et al. The use of del Nido cardioplegia in adult cardiac surgery: a prospective randomized trial. J Thorac Cardiovasc Surg 2018;155:1011-18.
27. Vistarini N, Laliberte E, Beauchamp P, Bouhout I, Lamarche Y, et al. Del Nido cardioplegia in the setting of minimally invasive aortic valve surgery. Perfusion 2017;32:112-7.
28. Hamad R, Nguyen A, Laliberte E, Bouchard D, Lamarche Y, et al. Comparison of del Nido cardioplegia with blood cardioplegia in adult combined surgery. Innovations (Phila) 2017;12:356-62.
29. Ziazadeh D, Mater R, Himelhoch B, Borgman A, Parker JL, et al. Single-dose del Nido cardioplegia in minimally invasive aortic valve

surgery. Semin Thorac Cardiovasc Surg 2017; pii: S0022-5223:31194-7.
30. Koeckert M.S., Smith DE 3rd, Vining PF, Ranganath NK, Beaulieu T, et al. Del Nido cardioplegia for minimally invasive aortic valve replacement. J Card Surg 2018;33:64-8.
31. Mishra P, Jadhav RB, Mohapatra CK, Khandekar J, Raut C, et al. Comparison of del Nido cardioplegia and St. Thomas Hospital solution-two types of cardioplegia in adult cardiac surgery. Kardiochir Torakochirurgia Pol 2016;13:295-9.
32. Li Y, Lin H, Zhao Y, Li Z, Liu D, et al. Del Nido cardioplegia for myocardial protection in adult cardiac surgery: a systematic review and meta-analysis. ASAIO J 2018;64:360-367.
33. Pragliola C, Hassan E, Al Otaibi K, et al. The del Nido cardioplegia in adult patients: simple reliable, effective-a propensity matched study of 102 patients with moderate o high Euroscore II.