Outcomes of Del Nido and hyperkalemic blood cardioplegia in adult cardiac surgery with prolonged aortic cross clamp times.

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Abstract:

Background

The utility and uptake of Del Nido cardioplegia in adult cardiac surgery is rapidly increasing. Cases with prolonged aortic cross clamp times necessitate multi dosing however an understanding of safe ischaemic times and definitive guidelines in this domain are lacking. Therefore, the aim of this study was to assess the safety and efficacy of our DNC strategy by comparing post-operative troponin profiles and clinical outcomes between del Nido and hyperkalaemic cardioplegia for cases with aortic cross clamp times of greater than 90 minutes.

Methods

A single centre, retrospective cohort study at Flinders Medical Centre and Flinders Private Hospital of patients undergoing composite cardiac surgery with a cross clamp time longer than 90 minutes. Data was prospectively collected from the Flinders Cardiac Surgery Registry from June 2014 to December 2022. A propensity matched (1:1) analysis was performed comparing patients receiving del Nido cardioplegia (n=194) to those receiving hyperkalemic blood cardioplegia (n=194). Primary outcome was the post-operative troponin release profile with clinical events reported as secondary outcomes .

Results

There was no difference in the peak or median troponin at 6, 12 and 72 hours nor number of patients with positive troponin profile post operatively between cohorts. There was no difference in clinical outcomes between groups with aortic cross clamp times of 90min which remained true in Sensitivity analysis extending out to 120min. The Del Nido cohort received less cardioplegia volume ($p < 0.001$) and were more likely to return to spontaneous rhythm ($p < 0.002$).

Conclusion

Del Nido cardioplegia for anticipated aortic cross clamp times of greater than 90min provided equivocal post operative troponin profiles and clinical outcomes compared to multidose hyperkalemic blood cardioplegia.

Keywords:

Cardioplegia, del nido, multi dose

Introduction

The use of Del Nido cardioplegia (DNC) as an alternative to hyperkalaemic crystalloid blood cardioplegia (HKB) is an accepted practice in cardiothoracic surgery (1). The use of single dose DNC for a cross clamp time of less than 90 minutes originates from paediatric cardiac surgery (2, 3). A single dose of DNC provides satisfactory myocardial protection for approximately 90 minutes (4). The use of single dose DNC in adult cardiac surgery with cross clamp times of less than 90 min is now supported by randomized control trials including that published by Ad et al (5). The recent prospective randomized trial by Garcia-Suarez included 474 patients in different settings of adult cardiac surgery not excluding complex procedures and showed comparable outcomes between HKB and DNC (6). The outcomes of multi dose DNC and determination of safe ischaemic time in adults and furthermore in adults with extended cross clamp time remains unclear. To date there is no clinical guideline supporting the delivery of DNC in cases with extended bypass times.

Current animal models and trials in explanted hearts have shown superior myocardial function and troponin profiles with single dose compared to multi dose DNC regiments (7, 8). There is also clear evidence of ischaemic changes inferenced by troponin profiles after 90 minutes of ischaemic conditions in these cohorts (7, 8). The existing literature on DNC in adults with cross clamp times over 90 minutes is currently limited to small patient cohorts or sub analyses of larger studies and interchangeably define aortic cross clamp time and ischaemic time making direct comparisons challenging (4, 9-16). Ross et al recently reported our unit's initial experience of DNC however only a small subset (40 patients) had aortic cross clamp times greater than 90 minutes in the DNC group (17), whilst Willekes et al have reported a propensity matched study of patients with prolonged aortic crossclamp times (18).

This study reports a review of the safety of DNC within our practice in patients with cross clamp time exceeding 90 minutes. We compared those who received HKB with those who received DNC. The primary aim was to assess safety and efficacy based on post operative Troponin T profile, with the secondary aim to compare post operative major adverse cardiac events between the two groups.

Methods

This is a single centre, retrospective cohort study including patients who underwent cardiac or aortic surgery with a cross clamp time longer than 90 minutes. Patients from both Flinders Medical Centre

and Flinders Private Hospital were included. Patient data was prospectively collected from the Flinders Cardiac Surgery Registry and the Australian New Zealand Collaborative Perfusion Registry from June 2014 to December 2022. During this interval 845 of 5094 patients had aortic cross clamp times greater than 90 min, of which 188 were excluded from the study (10 no cardioplegia data, 178 as outside of study period) (Figure 1). Ethics approval for this audit was granted by the Southern Adelaide Clinical Human Research Ethics Committee and the South Australia Local Health Network Office for Research (Quality Registry ID: 2265).

Patients were analysed according to their cardioplegia regimen of either HKB or DNC. DNC was introduced in November 2018. Clinical management, anaesthesia, composition and delivery methods of our DNC and HKB have been previously published (17). Specifically for DNC, after placement of the aortic cross clamp, cardioplegic arrest was induced with an antegrade induction dose of 1L delivered at flow rate of 200-300 ml/min at 6°C, targeting aortic root pressures >100mmHg and less than 150mmHg. This dose was followed by subsequent 500ml doses at sixty-ninety minute intervals delivered antegrade or retrograde as required. In cases of severe aortic regurgitation a combination of retrograde and ostial cardioplegia was used. Hyperkalaemic blood cardioplegic arrest was induced with tepid (34°C) hyperkalaemic blood/crystalloid cardioplegia (induction, 30 mmol/L) at induction and maintained with intermittent doses (maintenance, 15 mmol/L) every twenty-thirty minutes. Similar flows and pressures were targeted. In both groups, in addition to the timing of cardioplegia doses, the return of electrical or myocardial contractility were indications for re-dosing.

Definitions of clinical demography and outcomes were standardised on those reported by the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) National Database. Maximum ischemic time was defined as the maximum duration between completion of cardioplegia delivery and either the beginning of the next cardioplegia delivery or reperfusion with cross clamp removal; our data reflects expected redosing at >90 minutes in DNC and >30 minutes in HKB. Mortality was defined as death in hospital or within 30 days from surgery. Perioperative myocardial infarction was defined as having at least two of the following criteria: ΔTroponin T > 20 ug/L, new regional wall motion abnormalities on echocardiography, Q wave changes on electrocardiogram (ECG). A positive troponin profile was defined as having a troponin value at 72 hr following surgery which is the highest troponin measured within 72 hours of the index procedure. Acute kidney injury (AKI) was defined as postoperative creatinine greater than 150% baseline in accordance with the serum creatinine criteria of the renal Risk, Injury, Failure, Loss of renal function and End-stage renal disease (RIFLE) classification.

The registries meet the Australian Commission on Safety and Quality in Health Care National Operating Principles for Australian Clinical Quality Registries (https://www.safetyandquality.gov.au/publications-and-resources/resource-library/framework-australianclinical-quality-registries).
Database managers and staff meet weekly to undertake quality assurance processes. The unit's general anaesthetic, intraoperative monitoring, cardiopulmonary bypass (CPB), blood conservation and post-operative renal replacement protocols have been previously published (17).

Statistical Analysis

Patients that received DNC were 1:1 propensity matched without replacement with patients that received HKB, with cross clamp times greater than 90 minutes, providing 194 matched pairs. (Figure 1). Preoperative risk factor variables included in propensity matching were age, sex, diabetes, insulin dependent diabetes, chronic obstructive pulmonary disease, pulmonary hypertension, New York Heart Association classification, left ventricular dysfunction, emergency procedure, cerebrovascular disease, redo procedure, smoking history, elevated preoperative troponin, procedure type, cardiopulmonary bypass time, aortic cross clamp time, and procedure time.

A sensitivity analysis was performed on patients with cross clamp times greater 120 min yielding 64 matched pairs.

Stata v 15.1 (StataCorp LLC, Texas) was used for all statistical analyses. Pre-operative, intra-operative and post-operative outcomes were compared between the cohorts. Continuous variables are reported as median with interquartile range and are compared using the Wilcoxon rank-sum test. Categorical variables are reported as number of patients and group percentage and compared using the Fisher's exact test for variables with binary measures and Pearson's chi squared test for categorical variables. A p-value of <0.05 was considered statistically significant for all analyses without adjustment for multiple comparisons.

Equivalence in outcome for cardioplegia type was evaluated on the incidence of myocardial infarction, and positive troponin profile, and continuous postoperative troponin values at 6, 12 and 72 hrs, peak, and the 72 hr area under the curve, calculated based on the method described by Lakens using the two one-sided tests (TOST) procedure (4). Continuous troponin values underwent log transformation

to approximate normality. The TOST procedure utilised the Fishers exact Z-test for proportions. With upper and lower equivalence boundaries defined as Cohen's d ±0.3, to detect a type I error rate of 0.05 we had a power of 95% for myocardial infarction and 80% for peak postoperative troponin value between primary analysis groups.

Results

Patient Characteristics

5094 adult cardiac cases were performed between 12.6.2014 and 31.12.2022, with 845 having an AXC time of greater than 90 minutes. 657 patients were eligible for inclusion in propensity analyses (see consort diagram figure 1), resulting in 194 patients in each group for AXC time > 90min, and 64 patients in each group for the > 120min AXC time, with both cohorts demonstrating similar pre-operative characteristics respectively (Table 1 and 2).

Primary analysis

70% of cases in both groups were valve replacement or valve/coronary grafting surgery. There was no significant difference in total AXC time between the two groups. DNC was delivered at a colder temperature, requiring less volume and fewer doses of cardioplegia. Patients receiving HKB were more likely to receive combined antegrade and retrograde cardioplegia delivery. The maximum period of ischemia was significantly greater for DNC compared with HKB (98 (90, 109) vs 32 (28,36) p<0.001) and the spontaneous return of rhythm was more likely with the DNC compared to HKB (89% vs 59%, p<0.001) (Table 3).

Clinical outcomes were the same between DNC and HKB for rates of post-operative intra-aortic balloon pump (IABP), myocardial infarction, acute kidney injury, stroke, return to theatre, or mortality (Tables 4). The DNC had a higher rate of return to theatre for bleeding (6% vs 2%).

The median troponin value at time points 6, 12, and 72 hr post operatively, the maximum postoperative troponin, area under the curve nor the number of patients with positive troponin profile showed any difference between the two groups (Table 5/Figures 2), similarly there was no difference in time to peak troponin (Table 6). Equivalence testing found DNC to be equivalent to HKC for all troponin measures other than peak troponin (Table 5) (p=0.101).

Sensitivity analysis

Similar findings were found for the AXC time > 120-minute subgroup with no differences in preoperative characteristics and clinical outcomes (Tables 2, 7, 8). Troponin profiling did demonstrate differences, with the 72 hr, maximum postoperative troponin value and the area under the release curve being higher in the DNC group ($p<0.05$, Table 9, Figure 3). The median troponin profile at 6 and 12 hours, and the number of patients with positive troponin profile between cohorts were not different (Table 6). Equivalence testing found DNC to be not equivalent in troponin measures other than for positive troponin profile (Tables 9).

Discussion

Del Nido cardioplegia has a well-established safety profile in myocardial ischaemic times of up to 90 min (6), with current literature providing little consensus on management protocols for extended AXC times and optimal reporting of clinical endpoints (13, 20, 21). Clinical advantages of DNC compared to HKB are thought to be mediated by lidocaine's inhibition of cardiomyocyte sodium channels, prevention of hypertonic myocardial oedema moderated by mannitol and competitive inhibition of calcium influx by magnesium (7, 19). Comfortable dosing intervals, advantages over glycaemic control and reperfusion arrhythmias make it a popular alternative for myocardial protection (6). The continued reporting of clinical experiences is mandated to build an evidence base upon which practice may evolve.

Our results showed patients receiving DNC had significantly longer ischaemic time compared to the matched HKB group, while demonstrating increased rates of return of spontaneous activity, with no significant differences in clinical outcomes (Table 4). Whilst there was overall equivalence in myocardial injury as inferenced by post operative troponin T release (Table 5, 6) the optimal timing for DNC re-dosing and clinical endpoints for equivalence remain unclear. Sensitivity analysis of patients with cross clamp times of greater than 120 min similarly demonstrated no significant differences in clinical outcomes (Table 8) however troponin results were equivocal (Table 6, 9).

Troponin Profile

The post-operative release of high sensitivity troponin T is one measure reflecting the efficacy of myocardial protection and was chosen for this study due to its lower false positive rate compared to other biomarkers such as CKMB. Recent meta-analyses reporting troponin release in the setting of DNC are of limited value and provide little guidance on strategies for cases with extended AXC times (22, 23). In reporting the troponin T profile for DNC out to 72 hours we found equivalence in the median timepoint values and area under the curve between propensity matched groups in our primary analysis. This is in keeping with the initial single dose experience from our unit suggesting a robustness in the safety profile of our cardioplegia protocol despite DNC having threefold longer ischemic times (98 minutes vs 32 minutes) (17) and the recent report by Willekes et al (2024) (18) where they reported similar findings for patients with extended AXC times. The sensitivity analysis highlights the variation in redosing within this early experience with 25% of patients in the sub study receiving a single dose of DNC. In this cohort although troponin T profile values within 72 hrs were not equivalent, equivalence was observed in the incidence of positive troponin T at 72 hrs. With further ongoing evaluation the benefit of DNC may be ascertained.

The literature supporting multi-dose DNC is evolving, with reports in early studies of multi-dose DNC showing no difference in post-operative troponin T profile (10, 13), whilst Willekes (REF) showed lower release of Troponin T their functional assessments showed no differences between DNC and HKB. Other studies comparing DNC and HKB have also shown no difference however are limited by design bias (4,24). Existing literature reporting lower troponin profiles with DNC have also reflected concurrent reduction in AXC time (13,20). By comparison our study included as a variable in our propensity matching AXC time and this may explain troponin equivalence rather than reduction, even though DNC patients experienced longer ischaemic times. Our early (6 and 12hr) troponin T measurements are consistent with previously reported experiences of non-inferiority for DNC (5, 25). Ad et al, found lower and earlier peak troponin with DNC; in contrast Garcia-Suarez et al incorporated more diverse and complex procedures observing an earlier peak (<12hrs) with DNC (5, 6). In contrast to ours, their dosing strategy was a single 1000ml induction dose mixed with autologous blood (4:1 crystalloid: blood) followed by 500ml redosing for ischaemic periods >90 minutes or in patients with spontaneous activity (6).

Clinical Outcomes

Clinical outcomes of DNC in cases with prolonged AXC times and utilising multi-dose strategies varies in the literature (9, 10, 20-22, 26). Our study demonstrated no difference in post-operative major adverse events including transfusion, IABP use, maximum inotropic duration, myocardial infarction,

acute kidney injury, stroke or mortality. There was no difference in minimum haemoglobin suggesting there is no significant haemodilution with DNC. This was replicated in our sub group analysis which demonstrated equivalence in outcomes (Table 8), in keeping with a large cohort study sub-analysis done by Koda et al and the recently published prospective RCT by Garcia-Suarez et al however we did find a higher incidence of stroke with DNC (6, 9). In contrast other cohort studies have demonstrated a higher rate of IABP, stroke, and inotropic support and higher peak post-operative creatinine level in multi-dose DNC (13, 26). In this report it is significant that the median number of cardioplegia doses in the 90 minutes ACX time primary analysis was one therefore inference on multi-dosing may only be based on the sub-analysis.

In the primary analysis the preference for mode of cardioplegia delivery varied among our groups with DNC administered predominantly antegrade (75%) whilst HKB cardioplegia was delivered by combination antegrade and retrograde delivery in 64% of patients. This variation likely reflects the patient population chosen (those with prolonged cross clamp times) and the delivery strategy for multiple dose HKB frequently utilising a combined antegrade and retrograde delivery strategy in these patients. The significance of mode of re delivery is unclear and given high variability in existing literature, highlights the need for randomized controlled trials and standardized guidelines given variable clinical implementation. Expectedly the number of cardioplegia doses was 6 (HKB) compared to 1 (DNC) in the primary analysis and 7 (HKB) versus 2 (DNC) in the sensitivity analysis. The maximum ischaemic time was 32 and 98 minutes in the HKB and DNC groups reflecting our institutions redosing at approximately 30 and 90 minutes respectively.

The higher rate of return of spontaneous rhythm and lower need for defibrillation on removal of AXC in DNC is well reported (4, 6, 27-29). Our results showed the DNC cohort was more likely to return to spontaneous rhythm with multi-dose DNC regiments consistent in primary and sub analyses (Tables 3 and 7) and is consistent with findings our previously published experience (17).

Quality Improvement

There is no clear dosing regimen for extended cross clamp time and DNC use. Current protocols are based on experience, vary widely and make inter study comparisons challenging. The dosing regimens in the literature range from an initial dose of DNC of 1000-1200 mL with an additional maintenance dose of 300-1000 mL every 60 minutes after 90 minutes of cross clamp time (4-7,9-11,17).

Following our initial evaluation of DNC use, adjustments to practice were made and commonly a DNC dosing protocol with initiation with 1000 mL DNC induction dose followed by a further 500 mL DNC at 90 minutes ischemic time was utilised. Following evaluation of our current data, departmental morbidity and mortality reviews and recent publications discussing redosing and timing of DNC for cases with extended AXC (20, 21), we have developed our current multi dose DNC dosing protocol.

The current dosing protocol stipulates that when the total ischemic time is expected to be less than 90 minutes a single 1000 ml induction DNC dose is used. If the ischemic time is expected to exceed 90 minutes a 1000ml DNC induction dose is given followed by maintenance doses of 500ml DNC administered at approximately 60 minutes intervals thereafter.

Limitations

This is a retrospective observational study with inherent limitations associated with study design. Our report represents an evolving clinical practice reinforced by a culture of measurement and review, visible by multiple dosing protocol adjustments over time, with the most recent iteration of the delivery protocol being adopted in 2023. The choice of variables for the propensity matching is an inherent limitation of the statistical methodology, and additionally we have not performed sensitivity analyses on the route of cardioplegia administration or surgeon performing the procedure. The variation introduced by being unable to propensity match for surgeon is an inherent limitation of he retrospective study design. It is important to note the median number of cardioplegia doses in the 90 minutes ACX time primary analysis was one, therefore inference on multi-dosing is based on the sub-analysis alone. With regards to clinical outcomes one of the major concerns regarding multidose DNC is lidocaine toxicity and it's hypothesized results on myocardial contractility and arrhythmia. Arrhythmia and a quantitative reproducible measure of cardiac output such as inotropic requirements or cardiac index post operatively were not included. Similarly rates of return to theatre were higher in the DNC cohort however inferences on the manner and cause of this were not included. A further limitation is that we have not reported a 24 hr Troponin value as one of the two hospitals did not collect this time point, and our troponin profiles are not indexed to renal function nor type of procedure which can introduce confounders to their interpretation relative to these variables. Finally, a significant consideration is the learning curve for the operative team in adopting a new cardioplegic strategy, this will inadvertently introduce patient selection bias and additional confounders pertaining to timing of redosing, choice of cardioplegic agent, mode, and rate of delivery; which cannot be accounted for in a retrospective study design.

Conclusion

This is the largest quantitative cohort study on DNC use in patients with prolonged AXC time in Australia or New Zealand, and adds significantly to the limited international reports. Del Nido cardioplegia in more complex and longer procedures has demonstrated equivalent myocardial protection compared with multiple doses of HKB cardioplegia. This study is a quality assurance measure driven by clinical experience and our departmental morbidity and mortality review processes. Randomised, multi centre trials are needed to develop an evidence-based protocol for multi dose DNC.

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Tables:

Table 1: Patient demographics for aortic cross clamp time greater than 90 minutes.

		HKB	DNC	p-value
N		194	194	
Age		64 (52, 72)	64 (49, 73)	0.84
Male		135 (70%)	131 (68%)	0.66
Euroscore II		2 (1, 4)	2 (1, 4)	0.95
BMI		28 (25, 32)	29 (25, 32)	0.90
Diabetic		40 (21%)	42 (22%)	0.80
Insulin dependent		8 (4%)	11 (6%)	0.64
Baseline creatinine (umol/L)		87 (73, 104)	87 (71, 102)	0.91
Dialysis dependent		4 (2%)	3 (2%)	1.00
Pulmonary hypertension		15 (8%)	16 (8%)	1.00
COPD		41 (21%)	45 (23%)	0.62
Smoking history		105 (54%)	97 (50%)	0.42
PVD		8 (4%)	8 (4%)	1.00
Cerebrovascular Disease		15 (8%)	16 (8%)	1.00
Redo sternotomy		25 (13%)	23 (12%)	0.76
NYHA	1	75 (39%)	68 (35%)	0.36
	2	64 (33%)	74 (38%)	
	3	41 (21%)	32 (16%)	
	4	14 (7%)	20 (10%)	
LVEF	Normal	114 (59%)	110 (57%)	0.71
	Mild dysfunction	48 (25%)	56 (29%)	
	Moderate dysfunction	24 (12%)	23 (12%)	
	Severe dysfunction	8 (4%)	5 (3%)	
Baseline troponin T (ng/L)		49 (25%)	52 (27%)	0.73

Continuous variables are expressed median (IQR), categorical variables are expressed number (%).

Abbreviation: HKB: hyperkalaemic blood cardioplegia; DNC: del Nido cardioplegia; BMI: body mass index; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction.

Table 2: Subgroup analysis: Patient demographics for aortic cross clamp time greater than 120min.

Characteristic		**HKB**	**DNC**	**p-value**
N		64	64	
Age		57 (45, 72)	62 (45, 69)	0.83
Male		40 (63%)	46 (72%)	0.26
Euroscore II		2 (1, 5)	2 (1, 5)	0.92
BMI		27 (24, 30)	28 (24, 33)	0.40
Diabetic		11 (17%)	11 (17%)	1.00
Insulin dependent		5 (8%)	2 (3%)	0.44
Baseline creatinine (umol/L)		85 (69, 104)	85 (71, 104)	0.75
Dialysis dependent		1 (2%)	1 (2%)	1.00
Pulmonary hypertension		10 (16%)	9 (14%)	1.00
COPD		19 (30%)	19 (30%)	1.00
Smoking history		33 (52%)	34 (53%)	0.86
PVD		2 (3%)	0 (0%)	0.50
Cerebrovascular Disease		7 (11%)	8 (13%)	1.00
Redo sternotomy		10 (16%)	10 (16%)	1.00
NYHA Class	1	26 (41%)	20 (31%)	0.27
	2	18 (28%)	27 (42%)	
	3	15 (23%)	10 (16%)	
	4	5 (8%)	7 (11%)	
LVEF	Normal	41 (64%)	36 (56%)	0.83
	Mild dysfunction	15 (23%)	19 (30%)	
	Moderate dysfunction	6 (9%)	7 (11%)	
	Severe dysfunction	2 (3%)	2 (3%)	
Baseline troponin T (ng/L)		17 (27%)	18 (28%)	0.84

Continuous variables are expressed median (IQR), categorical variables are expressed number (%).

Abbreviation: HKB: hyperkalaemic blood cardioplegia; DNC: del Nido cardioplegia; BMI: body mass index; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction.

Table 3: Intraoperative variables for aortic cross clamp time greater than 90 minutes.

Variable		HKB	DNC	p-value
N		194	194	
Procedure type	CABG	30 (15%)	24 (12%)	0.72
	Aortic/Dissection	17 (9%)	21 (11%)	
	Other	10 (5%)	14 (7%)	
	Valve	90 (46%)	93 (48%)	
	Valve/CABG	47 (24%)	42 (22%)	
CPB time (min)		145 (125, 169)	143 (128, 171)	0.98
AXC time (min)		114 (102, 132)	112 (102, 129)	0.45
Total procedure time (min)		269 (229, 307)	266 (232, 320)	0.76
Hemofiltration requirement		7 (4%)	6 (3%)	1.00
Urine output (ml)		400 (220, 700)	400 (200, 750)	0.99
Minimum haemoglobin (g/L)		95 (81, 106)	90 (76, 103)	0.027
Minimum cardioplegia temperature (^{o}C)		31 (30, 31)	5 (5, 6)	<0.001
Total cardioplegia volume delivered (ml)		1885 (1550, 2249)	1009 (1004, 1381)	<0.001
Cardioplegia delivery route				
	Antegrade	70 (36%)	146 (75%)	<0.001
	Retrograde	0 (0%)	2 (1%)	
	Antegrade + Retrograde	124 (64%)	44 (23%)	
Number of cardioplegia doses		6 (5, 7)	1 (1, 2)	<0.001
Spontaneous recovery of rhythm		115 (59%)	170 (89%)	<0.001
Maximum ischemic time(min)		32 (28, 36)	98 (90, 109)	<0.001
Peak creatinine on pump (umol/L)		99 (82, 126)	101 (82, 134)	0.47
Last haemoglobin on pump(g/L)		96 (83, 108)	96 (86, 107)	0.80

Continuous variables are expressed median (IQR), categorical variables are expressed number (%).

Abbreviation: Abbreviation: HKB: hyperkalaemic blood cardioplegia; DNC: del Nido cardioplegia; CABG coronary artery bypass graft; CPB: cardiopulmonary bypass; AXC: aortic cross clamp.

Table 4: Post operative variables for aortic cross clamp time greater than 90 minutes.

Characteristic	HKB	DNC	p-value
N	194	194	
Mechanical ventilation (hr)	17 (8, 25)	18 (8, 27)	0.91
ICU stay (hr)	69 (43, 137)	70 (27, 120)	0.60
Hospital stay (d)	9 (7, 13)	10 (7, 14)	0.094
Mortality within 30 days	3 (2%)	8 (4%)	0.22
In hospital mortality	3 (2%)	8 (4%)	0.22
Return to theatre	3 (2%)	12 (6%)	0.017
Stroke	5 (3%)	4 (2%)	1.00
AKI	34 (18%)	39 (20%)	0.52
PRBC	72 (37%)	75 (39%)	0.69
MI	17 (9%)	15 (8%)	0.85
IABP	17 (9%)	10 (5%)	0.23

Continuous variables are expressed median (IQR), categorical variables are expressed number (%).

Abbreviations: HKB; hyperkalemic blood cardioplegia; DNC: Del Nido cardioplegia; ICCU: Intensive Critical Care Unit; AKI: acute kidney injury; PRBC: Any red blood cell transfusion; MI: myocardial infarction; IABP: intra-aortic balloon pump

Table 5. Post operative median troponin profiles for greater than 90 minutes Aortic Cross Clamp Time.

90 min Aortic Cross clamp		**HKB**	**DNC**	**p-value**	**Equivalency p-value**
N		194	194		
Troponin T (ng/L)	6hr	722 (411, 1196)	693 (430, 1237)	0.49	0.04
	12hr	735 (441, 1354)	783 (432, 1636)	0.60	0.025
	72hr	363 (242, 609)	408 (222, 860)	0.44	0.041
	max	780 (467, 1421)	834 (493, 1853)	0.26	0.081
	AUC	37616 (23601, 67166)	39586 (22865, 86359)	0.76	0.021
Positive troponin T rise		8 (5%)	8 (5%)	0.98	<0.001

Continuous variables are expressed median (IQR), categorical variables are expressed number (%).

Abbreviations: HKB: hyperkalemic blood cardioplegia; DNC: Del Nido cardioplegia; AUC: area under curve.

Table 6. Post operative peak troponin time as a function of cardioplegia type.

90 min Aortic Cross clamp		**HKB**	**DNC**	**p-value**
Patient proportion with peak Troponin T at time interval	6hr post op	63 (32%)	77 (40%)	0.26
	12hr post op	118 (61%)	102 (53%)	
	72hr post op	13 (7%)	15 (8%)	
120 min Aortic Cross clamp				
Patient proportion with peak Troponin T at time interval	6hr post op	15 (23%)	18 (28%)	0.83
	12hr post op	43 (67%)	40 (63%)	
	72hr post op	6 (9%)	6 (9%)	

Abbreviation: HKB: hyperkalaemic blood cardioplegia; DNC: del Nido cardioplegia; post op: post operative

Table 7. Subgroup analysis: Intraoperative variables for aortic cross clamp time greater than 120 minutes.

Variable		**HKB**	**DNC**	**p-value**
N		64	64	
Procedure type	CABG	5 (8%)	3 (5%)	0.77
	Aortic/Dissection	5 (8%)	9 (14%)	
	Other	6 (9%)	5 (8%)	
	Valve	33 (52%)	31 (48%)	
	Valve/CABG	15 (23%)	16 (25%)	
CPB time (min)		185 (160, 210)	190 (166, 217)	0.69
AXC time (min)		146 (129, 165)	143 (130, 173)	0.98
Total procedure time (min)		294 (248, 332)	322 (271, 375)	0.015
Hemofiltration requirement		0 (0%)	4 (6%)	0.12
Fluid output (ml)		400 (200, 750)	460 (250, 1188)	0.35
Minimum haemoglobin (g/L)		91 (77, 103)	91 (76, 101)	0.75
Minimum cardioplegia temperature (^{o}C)		31 (30, 31)	5 (5, 6)	<0.001
Total cardioplegia volume delivered (ml)		2129 (1950, 2486)	1523 (1007, 2009)	<0.001
Cardioplegia delivery route				
	Antegrade	30 (47%)	43 (67%)	0.031
	Retrograde	0 (0%)	1 (2%)	
	Antegrade + Retrograde	34 (53%)	20 (31%)	
Number of cardioplegia doses		7 (6, 8)	2 (1, 4)	<0.001
Spontaneous recovery of rhythm		36 (56%)	56 (89%)	<0.001
Maximum ischemic time (min)		32 (29, 39)	101 (87, 119)	<0.001
Peak creatinine on pump (umol/L)		101 (76, 135)	103 (83, 165)	0.22
Last haemoglobin on pump (g/L)		93 (80, 104)	94 (86, 105)	0.36

Continuous variables are expressed median (IQR), categorical variables are expressed number (%).

Abbreviation: Abbreviation: HKB: hyperkalaemic blood cardioplegia; DNC: del Nido cardioplegia; CABG coronary artery bypass graft; CPB: cardiopulmonary bypass; AXC: aortic cross clamp.

Table 8. Subgroup analysis: Post operative variables for aortic cross clamp time greater than 120 minutes.

Characteristic	HKB	DNC	p-value
N	64	64	
Mechanical ventilation (hr)	20 (12, 42)	20 (16, 68)	0.40
ICU stay (hr)	92 (45, 142)	90 (46, 186)	0.72
Hospital stay (d)	10 (7, 14)	10 (7, 15)	0.49
Mortality within 30 days	2 (3%)	4 (6%)	0.68
In hospital mortality	2 (3%)	4 (6%)	0.68
Return to theatre	1 (2%)	6 (10%)	0.049
Stroke	1 (2%)	2 (3%)	0.62
AKI	11 (17%)	16 (25%)	0.28
PRBC	26 (41%)	29 (47%)	0.49
MI	6 (9%)	11 (17%)	0.20
IABP	8 (13%)	4 (6%)	0.36

Continuous variables are expressed median (IQR), categorical variables are expressed number (%).

Abbreviations: HKB; hyperkalemic blood cardioplegia; DNC: Del Nido cardioplegia; ICCU: Intensive Critical Care Unit; AKI: acute kidney injury; PRBC: Any red blood cell transfusion; MI: myocardial infarction; IABP: intra-aortic balloon pump

Table 9. Sub analysis: Post operative median troponin profiles for 120 minutes Aortic Cross Clamp Time.

90 min Aortic Cross clamp		**HKB**	**DNC**	**p-value**	**Equivalency p-value**
N		64	64		
Troponin T (ng/L)	6hr	852 (427, 1455)	907 (593, 2095)	0.14	0.555
	12hr	1103 (528, 1795)	1220 (741, 3540)	0.11	0.63
	72hr	480 (287, 1015)	720 (372, 1878)	0.030	0.738
	max	1103 (498, 1845)	1406 (807, 3609)	0.019	0.837
	AUC	53428 (28151, 101896)	68633 (39815, 19209)	0.042	0.734
Positive troponin T rise		3 (5%)	0	0.074	<0.001

Continuous variables are expressed median (IQR), categorical variables are expressed number (%).

Abbreviations: HKB: hyperkalemic blood cardioplegia; DNC: Del Nido cardioplegia; AUC: area under curve.

Figures

Figure 1. Consort diagram. The 178 patients either had both DNC and HPK cardioplegia (55 cases) or were excluded as the surgeons performing operations did not use both cardioplegic techniques (112 cases). Abbreviations: DNC Del Nido cardioplegia, HKB hyperkalemic blood cardioplegia

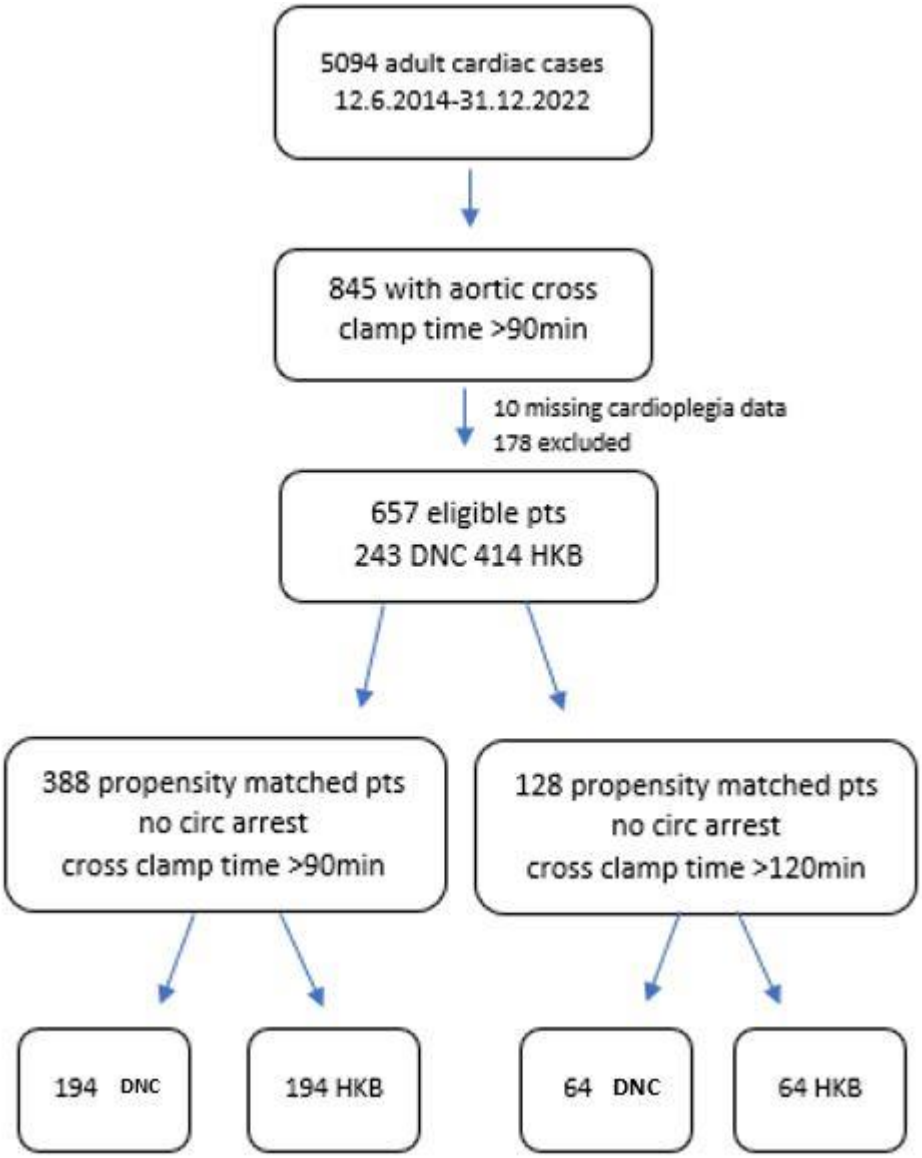

Figure 2. Box and whisker plot for Troponin profile based on cardioplegia strategy for greater than 90-minute ischaemic time. Solid middle baris the median, top and bottom of box the 75th and 25th percentile, with upper and lower adjacent values.

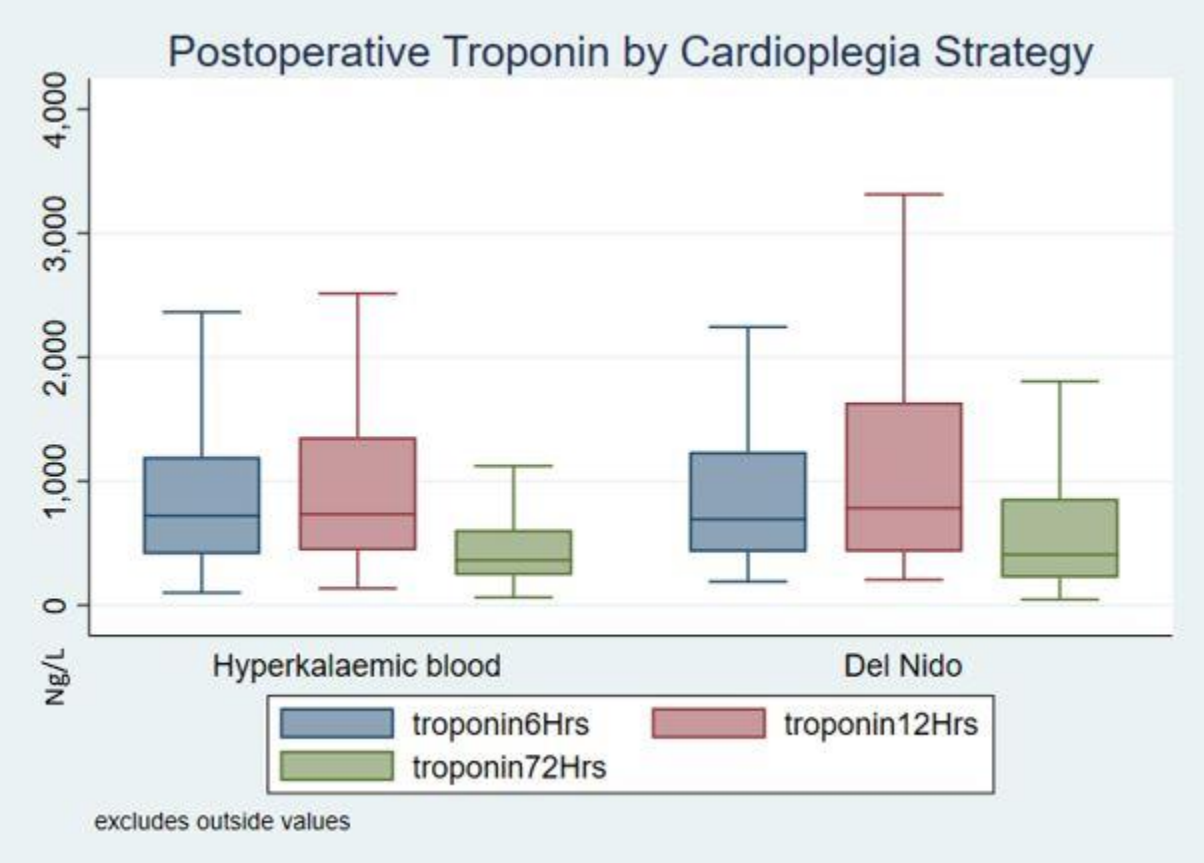

Figure 3. Troponin profile based on cardioplegia strategy for greater than 120minute ischaemic time. Solid middle baris the median, top and bottom of box the 75th and 25th percentile, with upper and lower adjacent values.