A novel dosing strategy of del Nido cardioplegia in aortic surgery

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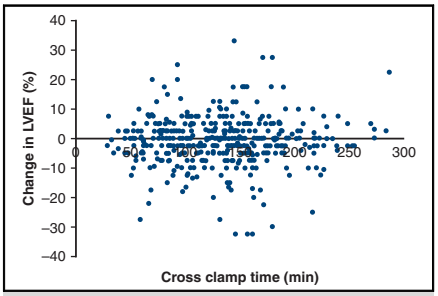
ABSTRACT

Objective: While del Nido (DN) cardioplegia is increasingly used in cardiac surgery, knowledge is limited in its safety profile for operations with prolonged crossclamp time (CCT). We have introduced a unique redosing strategy for aortic surgery: all operations use DN with a 1000-mL initiation dose (750 mL antegrade, 250 mL retrograde) composed of 1:4 blood:DN crystalloid. At 90 minutes CCT and every 30 minutes thereafter, a 250-mL dose was introduced retrograde in a 4:1 ("reverse") ratio. Additionally, at 90 minutes CCT and every 90 minutes thereafter, a reverse ratio dose of approximately 100 to 400 mL was introduced via the right coronary artery. Here, we analyze the outcomes of our unique redosing strategy used.

Methods: In total, 440 patients underwent aortic surgery between January 2015 and March 2021 under a single surgeon and received DN. Our primary end points were change in left ventricular ejection fraction (LVEF) and right ventricular systolic function based on echocardiography. Multivariable linear regression was used to analyze the relationship between CCT and outcomes.

Results: The median was 61 years old (interquartile range, 51-69), and 23% were female. Indication was aneurysm in 65% and dissection in 24%. Median preoperative LVEF was 60% (55%-62%). Median CCT and cardiopulmonary bypass times were 135 minutes (93-165 minutes) and 181 minutes (142-218 minutes), respectively. In-hospital mortality occurred in 3%. Multivariable linear regression showed CCT was not associated with change in LVEF or change in right ventricular systolic function.

Conclusions: Our unique method of redosing DN cardioplegia appears to provide safe and effective myocardial protection for aortic surgery. (JTCVS Open 2022;10:39-61)



Our dosing strategy shows no association between change in LVEF and crossclamp time.

CENTRAL MESSAGE

Using our dosing strategy, which introduces "reverse ratio" 4:1 blood:del Nido crystalloid, del Nido cardioplegia is safe in aortic surgery, including cases with prolonged myocardial ischemic time.

PERSPECTIVE

The safety of del Nido cardioplegia had not yet been widely studied in complex cardiac surgery with prolonged clamp times. By describing a dosing method and showing clinical outcomes from cases with crossclamp times between 30 minutes to 280 minutes, surgeons may more confidently adopt del Nido cardioplegia for a wider variety of cases.

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Abbreviations and Acronyms

CCT = crossclamp time
CI = confidence interval
DN = del Nido
ICU = intensive care unit
IQR = interquartile range
LVEF = left ventricular ejection fraction
RVSF = right ventricular systolic function
TEE = transesophageal echocardiogram
TTE = transthoracic echocardiogram
VIS = vasoactive inotropic score

Video clip is available online.

There are many different cardioplegia solutions of varying compositions used for myocardial arrest and protection in cardiac surgery, and the choice of cardioplegia is often up to institution or surgeon preference. Most conventional blood cardioplegia requires a dose every 15 to 20 minutes. del Nido (DN) cardioplegia solution was originally developed for pediatric and congenital heart surgery and was widely adopted for its ability to provide myocardial protection for 90 minutes after a single induction dose.[1,2] The solution uses lidocaine and magnesium to arrest the myocardium in a depolarized state.

More recently, DN cardioplegia has been used in adult cardiac surgery, and its safety compared with conventional cardioplegia solutions has been documented in adult operations including coronary artery bypass graft,[3-6] valve operations,[3,7-11] reoperative aortic valve surgery,[12] and more recently ascending aortic surgery.[13] In operations with prolonged crossclamp time (CCT), however, there is no consensus regarding timing, quantity, and route of additional doses.[14] By our knowledge, fewer than 40 operations using DN with CCT greater than 3 hours have been shared in literature.

In a study by Lenoir and colleagues[11] on aortic root surgery with CCTs up to 4 hours, patients in their DN group had greater cardiac biomarkers after 150 minutes of ischemic time compared with their conventional cardioplegia group. In their methods for operations that appeared to exceed 90 minutes of CCT, DN cardioplegia was administered with a 1250-mL antegrade initiation dose in a 1:4 ratio of blood to DN crystalloid, with an additional dose administered at 60 minutes, again in a 1:4 ratio. The authors rationalized the increased biomarkers in the DN cohort by citing literature that showed that repeated doses of DN cardioplegia may lead to reduced cardiac functional recovery and negative inotropic effects, speculating that this effect may be due to myocardial concentration of lidocaine.[15] In contrast, a study on ascending aortic surgery showed no difference in postoperative biomarkers between blood and DN cardioplegia; their DN redosing strategy included additional doses in 1:4 ratio every 60 minutes.[13]

Although DN cardioplegia continues to be administered in adult cardiac operations, there still exists a well-grounded hesitancy to use it for prolonged complex cases. We developed a unique method of dosing DN cardioplegia, which was used in aortic operations with myocardial ischemia times up to 280 minutes. The present study aimed to analyze postoperative outcomes of these cases to assess its safety and effectiveness of the DN dosing strategy. We hypothesized that the described method of redosing DN cardioplegia would be safe for aortic surgery.

METHODS

Ethical Statement

This protocol (#AAAR2949) was approved by the Columbia University Irving Medical Center institutional review board with waiver of patient consent on December 14, 2021.

Patients

All patients who underwent open thoracic aortic surgery by a single surgeon (H.T.) at our Aortic Center between January 2015 and March 2021 were included. Patients were excluded if they did not receive a full first dose of cardioplegia (n = 20) or if they received systemic potassium as their first dose (n = 6). The final study cohort was 440 patients (Figure E1). Patient demographics, operative details, and postoperative outcomes were obtained from our Aortic Center database and review of electronic medical records. Cardioplegia characteristics were obtained from our institutional perfusion database. To better describe the clinical characteristics of the study cohort based on the redosing strategy delineated herein, the patients were divided into 3 groups based on CCT: CCT <90 minutes (n = 100), CCT 90 ≤ X < 180 minutes (n = 268), and CCT ≥ 180 minutes (n = 72).

To better understand the safety of this dosing strategy on an "unremarkable heart," a subgroup analysis was conducted of patients who had undergone isolated aortic operation without any concomitant cardiac operation or any pre-existing functional or structural heart disease. For this group, patients with a preoperative left ventricular ejection fraction (LVEF) <50%, decreased preoperative right ventricular systolic function (RVSF), moderate or severe valvulopathy, history of coronary artery disease, or previous cardiac intervention were excluded, leaving a subset of 110 patients in the "isolated aortic disease" subgroup (Figure E1).

Surgical Technique

Surgical indication was determined based on most recent guidelines.[16,17] An open aneurysm repair was recommended for patients with aneurysms ≥55 mm and recommended for some patients based on individual risk assessment for aneurysms 50 to 55 mm. Patients with aneurysms 45 to 50 mm may be offered a repair at a concomitant open cardiac procedure. Acute type A dissections were repaired with emergent surgery. The aortic valve was spared during aortic root replacement with reimplantation techniques whenever appropriate.[18-20] When replacement was necessary, the prosthetic valve was chosen based on guidelines and patient preference. Supra-aortic vessels were individually reconstructed using a multibranch graft. The arterial cannulation site was typically placed in the distal ascending aorta with the option of using the axillary artery, based on surgeon preference and aortic pathology. Femoral cannulation was considered

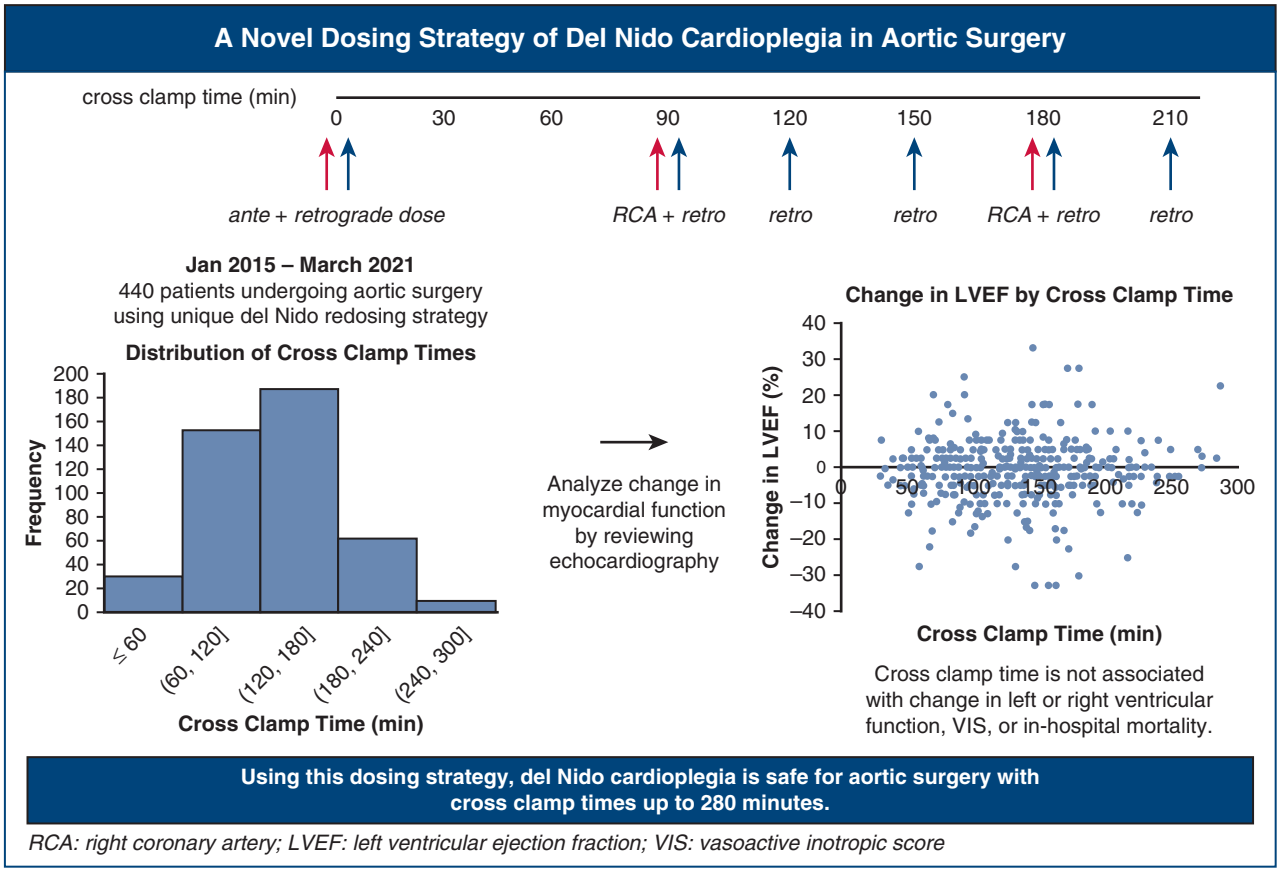

FIGURE 1. Our dosing strategy uses del Nido cardioplegia and features redoses starting at 90 minutes of myocardial ischemic time and every 30 minutes thereafter. Based on our study of 440 patients undergoing aortic surgery, del Nido cardioplegia appears to provide safe and effective myocardial protection for aortic operations up to 280 minutes of crossclamp time. *RCA*, Right coronary artery; *LVEF*, left ventricular ejection fraction; *VIS*, vasoactive inotropic score.

to be the last option. Distal aortic anastomosis in arch replacement procedures was performed under moderate hypothermia (24-28 °C, based on nasopharyngeal temperature) and with bilateral antegrade cerebral perfusion.

All operations used DN cardioplegia via the following protocol, visualized in Figure 1 and Video Abstract. At the time of the aortic crossclamp, a 1000-mL initiation dose composed of 1 part patient blood to 4 parts DN crystalloid was introduced, 750 mL antegrade through the aortic root (or directly through the coronary ostia if significant aortic insufficiency was present) and 250 mL retrograde through the coronary sinus. After 90 minutes of crossclamp time and every 30 minutes thereafter, a 250-mL dose was introduced retrograde in a 4:1 blood:DN crystalloid "reverse ratio." In addition, at 90 minutes of crossclamp time and every 90 minutes thereafter, a 4:1 reverse ratio dose was introduced via the right coronary artery for 2 minutes at a line pressure of 200 mm Hg (approximately 100-400 mL). Topical cooling was not used. A left ventricular vent was used in all cases.

The composition of DN cardioplegia in both 1:4 standard ratio and 4:1 reverse ratio compared to standard cardioplegia is displayed in Table E1. Standard ratio was used in initiation doses to induce arrest with sufficient hyperkalemia and lidocaine. Reverse ratio was used at our institution after literature suggested that lidocaine in cardioplegia may accumulate to toxic levels if continually dosed.[15,21] After careful calculation, we found that reversing the ratio to 4:1 blood:DN crystalloid for maintenance doses lowered the amount of lidocaine while also providing enough cardioplegia to maintain myocardial quiescence.

Study End Points

The primary outcomes of interest were change in LVEF and change in RVSF comparing preoperative and postoperative values, measured from echocardiography. Transthoracic echocardiogram (TTE) was used if available, and data were supplemented from intraoperative transesophageal echocardiogram (TEE) if TTE data was insufficient or missing (Table E2). Preoperative values were obtained from TTE done closest to the date of operation. The median and interquartile range (IQR) days between preoperative TTE and date of operation was 43 days (6-113 days) for our cohort. Postoperative values were obtained from predischarge TTE, with a median and IQR of 6 days (4-11 days) between operation and predischarge TTE. Nearly all (413/415, 99.5%) predischarge echo reports were official reading from the Columbia University Irving Medical Center Cardiac Echo Laboratory, which regularly monitors for quality and interobserver variability and were read in accordance with American Society of Echocardiography criteria. Although one half (n = 235, 53%) of the preoperative TTE reports were from the same Columbia University Irving Medical Center laboratory, the rest were scanned from outside cardiologists, including 8% (n = 37) of reports from Columbia- or New York Presbyterian–affiliated sources. In the cases that LVEF was reported as a range, the average of the range was used. Eight patients (1.8%) did not

have LVEF data on either preoperative and/or predischarge echocardiogram and thus were excluded from the analysis of change in LVEF (Table E3). For change in RVSF, 42 patients (9.5%) were excluded since they did not have data on preoperative and/or postoperative echocardiogram (Table E4).

Secondary outcomes were in-hospital mortality, vasoactive inotropic score (VIS) at intensive care unit (ICU) admission, and uneventful recovery. VIS is a weighted sum of inotropes and vasoconstrictors such as dobutamine and norepinephrine and is a known predictor of mortality and morbidity after cardiac surgery.[22] Uneventful recovery is a binary composite end point describing any patient discharged from the hospital without in-hospital mortality, any stroke, reoperation for bleeding, respiratory failure, acute renal failure, deep sternal infection, postcardiotomy shock, or permanent pacemaker implantation in the postoperative period.[23]

Data Definitions

Change in LVEF was calculated as the difference between the postoperative LVEF and the preoperative LVEF. RVSF was reported categorically on echocardiogram on an ordinal scale ranging from normal, mildly decreased, mildly to moderately decreased, moderately decreased, moderately to severely decreased, to severely decreased. Change in RVSF was defined as the number of categories changed from the preoperative RVSF to the postoperative RVSF and could be zero (for no change), positive (for increased RVSF after operation), or negative (for decreased RVSF). Stroke, reoperation for bleeding, respiratory failure, acute renal failure, and deep sternal infection were consistent with the definitions of the Society of Thoracic Surgeons Adult Cardiac Surgery Database.[24] Postcardiotomy shock was defined as any patient requiring extracorporeal membrane oxygenation in the postoperative period.

Statistical Analysis

R version 4.0.4 statistical software (R Foundation for Statistical Computing) was used for all analysis. Patient characteristics were analyzed using the 'tableone' package. Continuous variables were all found to be non-normally distributed by the Shapiro–Wilks Test, and were expressed as median (IQR) and analyzed by Kruskal–Wallis test. Categorical variables were expressed as a percentage and were compared using the χ^2 test. Outcomes were analyzed against the independent variable crossclamp time as a continuous variable in all regression models, even though crossclamp time was categorically divided into groups in Tables 1-3 for descriptive purposes. Change in RVSF was calculated as a continuous variable and analyzed with linear regression.[25] Multivariable linear regression was used to analyze continuous outcomes (change in LVEF, change in RVSF, and VIS), whereas multivariable logistic regression was used to analyze binary outcomes (in-hospital mortality and uneventful recovery). For multivariable analysis, independent variables were selected based on clinical significance and previous literature; variable selection was additionally informed by variables with an alpha of ≤ 0.10 on univariable analysis. The 'rms' package was used to analyze the binary outcomes and to create cubic spline figures with 3 knots after adjusting for covariates. Missing data was equal to or less than 10% in all variables and was excluded from analyses (Table E5).

RESULTS

Preoperative patient characteristics are described in Table 1 for the total cohort and shown in groups according to crossclamp time (n = 440). Compared with the 100 patients whose crossclamp time was less than 90 minutes, the patients with the longest crossclamp times ($\geq$180 minutes, n = 72) were younger in age (56 vs 66, $P < .001$), had greater body surface area (2.17 vs 1.91, $P < .001$), had a greater incidence of preoperative aortic insufficiency (33% vs 11%; $P < .001$), and had a greater history of infective endocarditis (17% vs 2%, $P < .001$). Overall, the most common primary indication for surgery was aneurysm in 288 (65%) patients. Dissection (n = 106, 24%) and valvulopathy (n = 28, 6%) were the next most common; the remaining handful of cases had a primary indication of infection, hematoma, or obstruction.

Figure 2 shows the distribution of crossclamp times of the cohort. The operative characteristics are shown in Table 2. The median was 135 minutes with an IQR of 93-165. One half (n = 219, 50%) required the use of circulatory arrest. Only 12 (3%) patients had isolated ascending arch replacement, and nearly one half (n = 205, 47%) had proximal extension including valve-sparing root replacement, Bentall, or procedure of the aortic valve. The remaining patients had a procedure with either a distal extension (n = 98, 22%) or both proximal and distal extensions (n = 125, 28%). The most common additional procedures were coronary artery bypass graft (n = 78, 18%) and mitral valve procedures (n = 30, 7%).

Primary Outcomes

The median change in LVEF was 0% (IQR –5 to 2.5), with 79 (18%) of patients having no change in LVEF, 161 (37%) improving in LVEF, and 191 (43%) decreasing. On multivariable linear regression adjusting for preoperative LVEF and chronic lung disease, there was no significant relationship between CCT and change in LVEF (coefficient estimate = 0.001, 95% confidence interval [CI], −0.013 to 0.015, $P = .879$; Figure 3, *A*, Table E6). There was no relationship between CCT and change in LVEF after excluding patients with preoperative aortic valvulopathy and who underwent an aortic valve operation (Figure E2). Because circulatory arrest may contribute some hypothermia and thus extra myocardial protection, the primary outcomes were also studied in patients that did not have circulatory arrest (n = 221, 50%). In patients without circulatory arrest, crossclamp time was not a predictor in change in LVEF ($P = .119$) (Figure E3, *A*).

Most patients (n = 292, 66%) did not have a change in RVSF on echocardiography after the operation. Nearly 1 in 5 (n = 84, 19%) of patients had decreased RVSF after operation; 5% (n = 22) had increased RVSF. In univariate analysis on change in RVSF, preoperative RVSF, sex, history of diabetes, and urgent or emergent operation status were identified to be have an association with an $\alpha < 0.10$. On multivariable linear regression adjusting for these 4 covariates, there was no relationship between CCT and change in RVSF (coefficient estimate = 0.001, 95% CI, –0.001 to 0.003, $P = .204$; Figure 3, *B*, Table E6). In patients without circulatory arrest, crossclamp time was found to be a predictor in change in RVSF ($P = .004$; Figure E3, *B*).

TABLE 1. Patient characteristics by crossclamp time

Patient characteristics	All patients (n = 440), N (%) median [IQR]	CCT <90 min (n = 100), N (%) median [IQR]	CCT 90 <X < 180 min (n = 268), N (%) median [IQR]	CCT ≥180 min (n = 72), N (%) median [IQR]	*P* value
Age	61 [51-69]	66 [58-75]	60 [49-69]	56 [46-62]	<.001*
Female	100 (23)	50 (50)	46 (17)	4 (6)	<.001*
BSA	2.04 [1.88-2.20]	1.91 [1.75-2.13]	2.05 [1.91-2.21]	2.17 [2.01-2.33]	<.001*
Hypertension	325 (74)	84 (84)	193 (72)	48 (67)	.021*
On dialysis	5 (1)	1 (1)	1 (0)	3 (4)	.068
Diabetes	61 (14)	19 (19)	30 (11)	12 (17)	.118
Endocarditis	25 (6)	2 (2)	11 (4)	12 (17)	<.001*
CLD	57 (13)	11 (11)	40 (15)	6 (8)	.269
CVD	50 (11)	15 (15)	26 (10)	9 (13)	.343
PVD	103 (23)	23 (23)	60 (22)	20 (28)	.628
Preoperative LVEF	60 [55-62]	60 [55-62.5]	60 [52.5-62.5]	57.5 [54-60]	.524
Low EF (<40%)	32 (7)	3 (3)	27 (10)	2 (3)	.018*
Moderate or severe AS	61 (14)	18 (18)	39 (15)	4 (6)	.058
Moderate or severe AI	119 (27)	11 (11)	84 (31)	24 (33)	<.001*
Primary indication					
Aneurysm	288 (65)	61 (61)	184 (689)	43 (60)	.208
Dissection	106 (24)	28 (28)	62 (23)	16 (22)	.575
Valvular	28 (6)	7 (7)	16 (6)	5 (7)	.915
Obstruction	2 (0)	1 (1)	0 (0)	1 (1)	.195
Infection	11 (2)	2 (2)	4 (2)	5 (7)	.029*
Hematoma	6 (1)	2 (2)	3 (1)	1 (1)	.810
Urgent/emergent	214 (49)	45 (45)	141 (53)	28 (39)	.084

CCT, Crossclamp time; *IQR*, interquartile range; *BSA*, body surface area; *CLD*, chronic lung disease; *CVD*, cerebrovascular disease; *PVD*, peripheral vascular disease; *LVEF*, left ventricular ejection fraction; *EF*, ejection fraction; *AS*, aortic stenosis (moderate or severe); *AI*, aortic insufficiency (moderate or severe). **P* value < .05.

Secondary Outcomes

More than three-quarters (n = 335, 76%) of the total cohort were on inotropes or vasopressors upon admission to the ICU, with a median VIS of 4.94 (1.05-10.22) (Table 3). Patients with longer crossclamp times had a greater percentage of inotrope use and greater VIS at time of ICU admission. In analyzing the effect of CCT on VIS, the following variables were selected for multivariate analysis based on clinical importance: age, infective endocarditis, chronic lung disease, cerebrovascular disease, cardiopulmonary bypass time, preoperative LVEF, primary indication of dissection, and urgent or emergent operation status. After adjusting for these covariates, there was no relationship between CCT and VIS (coefficient estimate = −0.016, 95% CI, −0.041 to 0.008, $P = .195$) (Figure 4, *A*, Table E6).

In-hospital mortality occurred in 11 patients (3%). There was no relationship between CCT and in-hospital mortality on multivariable logistic regression controlling for age and preoperative LVEF (odds ratio, 0.991; 95% CI, 0.997-1.006; $P = .250$) (Figure 4, *B*, Table E7).

As shown in Table 3, most (n = 276, 63%) patients had an uneventful recovery. In multivariable logistic regression, the odds ratio of uneventful recovery decreased with crossclamp time after controlling for the same covariates as VIS (odds ratio, 0.993; 95% CI, 0.988-0.997: $P = .002$) (Figure 4, *C*, Table E7). Incidence of pacemaker implantation, respiratory failure, and postcardiotomy shock were increased in patients with the greatest crossclamp times and were likely drivers of the relationship between crossclamp time and uneventful recovery. We reviewed patients with postcardiotomy shock to understand its increased incidence in the group with longer crossclamp times and found that the clamp time was rather prolonged by intraoperative technical challenges and deemed not to be due to issues with cardioplegia (Table E8).

Subgroup Analysis

Preoperative characteristics, operative details, and postoperative outcomes for the isolated aortic disease subgroup are shown in Table E9. The subgroup with isolated aortic disease (n = 110) had lower rates of cerebrovascular disease

TABLE 2. Operative details by crossclamp time

Operative detail	All patients (n = 440), N (%) median [IQR]	CCT <90 min (n = 100), N (%) median [IQR]	CCT 90 < X < 180 min (n = 268), N (%) median [IQR]	CCT ≥180 min (n = 72), N (%) median [IQR]	*P* value
Ascending only	12 (3)	9 (9)	3 (1)	0 (0)	<.001*
Proximal extension	205 (47)	30 (3)	137 (51)	38 (53)	.001*
VSRR	84 (19)	1 (1)	63 (24)	20 (28)	<.001*
Bentall	82 (19)	9 (9)	55 (21)	18 (25)	.013*
AV procedure	39 (9)	20 (2)	19 (7)	0 (0)	<.001*
Distal extension	98 (22)	56 (56)	42 (16)	0 (0)	<.001*
Hemiarch	22 (5)	15 (15)	7 (3)	0 (0)	<.001*
Partial/total	76 (17)	41 (41)	35 (13)	0 (0)	<.001*
Proximal + distal	125 (28)	5 (5)	86 (32)	34 (47)	<.001*
Root + hemiarch	17 (4)	1 (1)	12 (5)	4 (6)	.219
Root + partial/total	23 (5)	0 (0)	13 (5)	10 (14)	<.001*
AVR + hemiarch	45 (10)	3 (3)	31 (12)	11 (15)	.016*
AVR + partial/total	40 (9)	1 (1)	30 (11)	9 (13)	.006*
Additional procedures					
Mitral valve	30 (7)	1 (1)	19 (7)	10 (14)	.004*
Tricuspid	9 (2)	1 (1)	6 (2)	2 (3)	.674
CABG	78 (18)	12 (12)	45 (17)	21 (29)	.012*
CPB time, min	180 [142-217]	123 [96.5-165]	179 [154-204]	261 [230-295]	<.001*
CCT, min	135 [93-164]	72 [59-80]	138 [113-156]	206 [189-225]	<.001*
Circulatory arrest	219 (50)	56 (56)	129 (48)	34 (47)	.363

"Partial/total" indicates partial or total arch replacement. *CCT*, Crossclamp time; *IQR*, interquartile range; *VSRR*, valve-sparing root replacement; *AV*, aortic valve; *AVR*, aortic valve replacement; *CABG*, coronary artery bypass graft; *CPB*, cardiopulmonary bypass. **P* value < .05.

(n = 5, 5%) when compared with the remaining 332 patients (n = 45, 14%, $P = .015$), and otherwise was not different in terms of preoperative characteristics aside from the variables selected in creating the subgroup. The distribution of crossclamp times is shown in Figure E4 and was not different from the remaining patients

TABLE 3. Postoperative outcomes by CCT

Postoperative outcome	All patients (n = 440), N (%) median [IQR]	CCT <90 min (n = 100), N (%) median [IQR]	CCT 90 < X < 180 min (n = 268), N (%) median [IQR]	CCT ≥180 min (n = 72), N (%) median [IQR]	*P* value
Inotropes on ICU admittance	335 (76)	67 (67)	204 (76)	64 (89)	.004*
VIS on ICU admission	4.94 [1.05-10.22]	3.3 [0-9.2]	4.5 [1.1-9.5]	7.6 [3-12.9]	.001*
Length of ICU stay, d	3 [1.6-6.1]	2.9 [1.4-5.6]	2.8 [1.5-5.9]	4.7 [2.3-9.6]	.004*
Length of hospital stay, d	8 [6-14]	9 [6-15]	8 [6-13]	10 [7-21]	.020*
Uneventful recovery	276 (63)	70 (70)	172 (64)	34 (47)	.007*
In-hospital mortality	11 (3)	4 (4)	5 (2)	2 (3)	.500
Re-exploration for bleed	22 (5)	4 (4)	13 (5)	5 (7)	.672
Pacemaker implantation	30 (7)	2 (2)	19 (7)	9 (13)	.025*
Respiratory failure	128 (29)	25 (25)	71 (27)	32 (44)	.007*
Stroke	26 (6)	9 (9)	10 (4)	7 (10)	.053
Acute renal failure	27 (6)	4 (4)	19 (7)	5 (7)	.672
Deep sternal infection	4 (1)	2 (2)	1 (0)	1 (1)	.307
Postcardiotomy shock	15 (3)	2 (2)	7 (3)	6 (8)	.040*
Change in LVEF (%)	0 [−5 to 2.5]	0 [−4.88 to 2.5]	5 [−5 to 2.5]	0 [−2.5 to 2.6]	.546
Decrease in RVSF	85 (21)	18 (20)	57 (24)	10 (15)	.333

CCT, Crossclamp time; *IQR*, interquartile range; *ICU*, intensive care unit; *VIS*, vasoactive inotropic score; *LVEF*, left ventricular ejection fraction; *RVSF*, right ventricular systolic function. **P* value < .05.

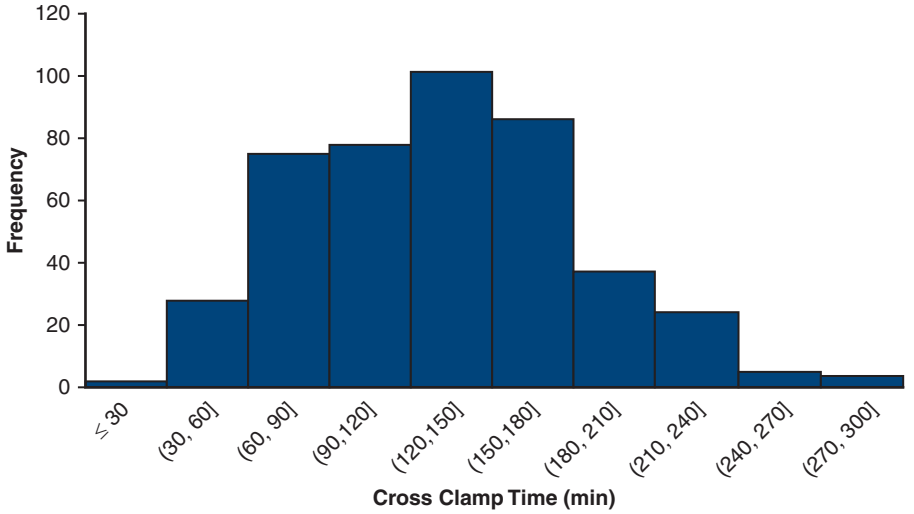

FIGURE 2. Distribution of crossclamp times of 440 aortic surgery patients receiving del Nido cardioplegia, including cases between 27 minutes and 278 minutes.

(133 minutes vs 135 minutes, $P = .335$), although cardiopulmonary bypass time was shorter in this subgroup (171 minutes vs 185 minutes, $P = .030$).

In the postoperative period, the isolated aortic disease subgroup had lower VIS at ICU admission (3.14 vs 5.24, $P = .003$), shorter ICU stays (2.0 days vs 3.4 days, $P = .006$), and shorter hospital stays (7 days vs 9 days, $P = .001$). There was also lower incidence of permanent pacemaker implantation (2% vs 9%, $P = .029$) and respiratory failure (16% vs 33%, $P = .001$) postoperatively, contributing to a greater rate of uneventful recovery (79% vs 57%, $P < .001$). Although the subgroup had comparable changes in LVEF, there was a lower incidence of decreased RVSF after operation (14% vs 24%, $P = .054$). There was no relationship between crossclamp time and change in LVEF ($P = .324$), change in RVSF ($P = .234$), or VIS ($P = .562$) (Table E10) in multivariable linear regression. Unlike the whole cohort, there was no relationship between crossclamp time and uneventful recovery in this subgroup ($P = .662$) (Table E10).

DISCUSSION

The present study examined the utility of a unique dosing strategy for DN cardioplegia in aortic surgery. We observed no difference in primary outcomes of change in LVEF and change in RVSF, as well as no difference in VIS score at

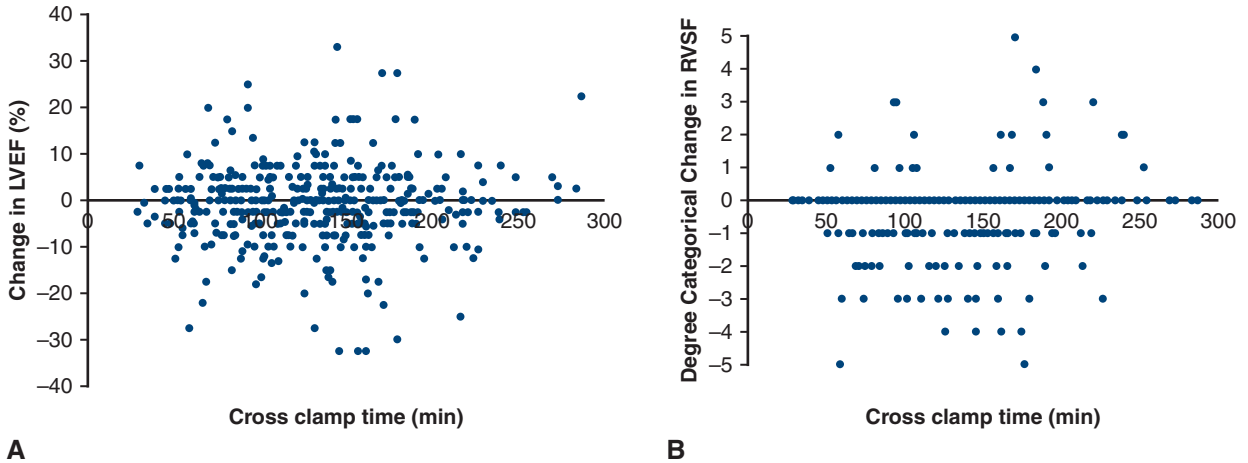

FIGURE 3. Change in left ventricular ejection fraction (A) and change in right ventricular systolic function (B) against crossclamp time for 440 patients undergoing aortic surgery using the described del Nido dosing technique. There was no relationship between crossclamp time and change in LVEF ($P = .879$) or change in RVSF ($P = .204$) after multivariable linear regression. *LVEF*, Left ventricular ejection fraction; *RVSF*, right ventricular systolic function.

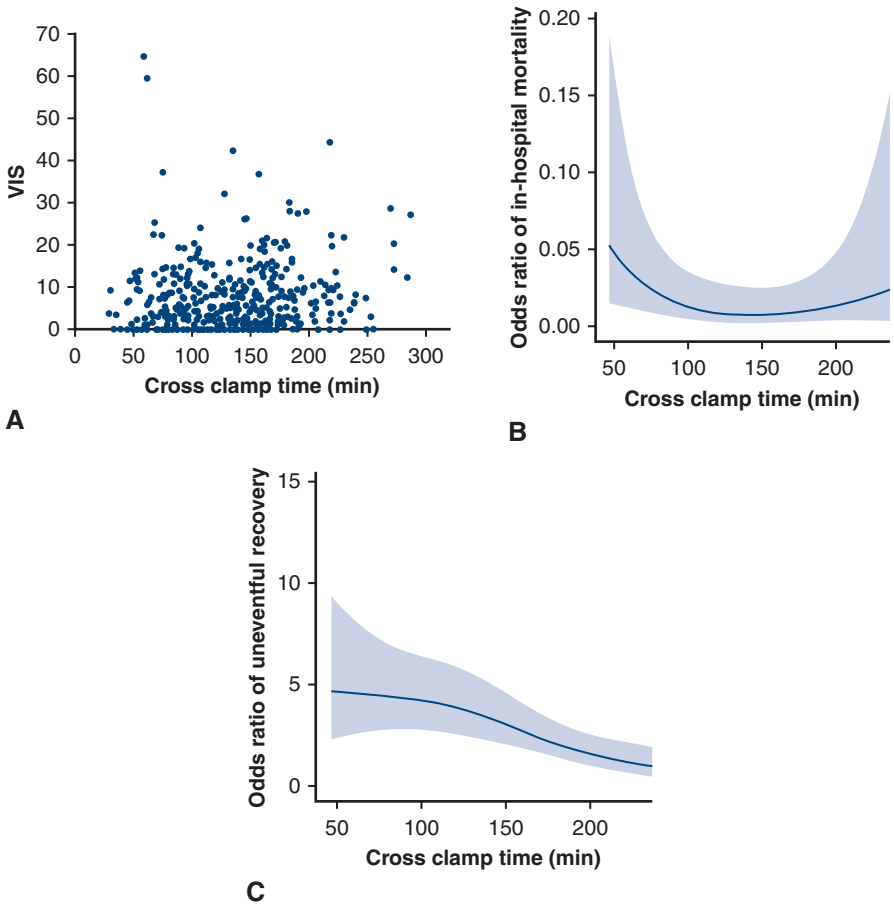

FIGURE 4. Vasoactive inotropic score (*VIS*) (A), odds ratio of in-hospital mortality (B), and odds ratio of uneventful recovery (C) by crossclamp time for 440 patients undergoing aortic surgery using the described del Nido dosing technique. There was no relationship between crossclamp time and VIS after multivariable linear regression ($P = .195$) or crossclamp time and in-hospital mortality after multivariable logistic regression ($P = .250$) Crossclamp time was found to be a predictor of uneventful recovery after adjusting for covariates ($P = .002$).

ICU admission and in-hospital mortality across CCT with our dosing strategy. While the odds ratio of uneventful recovery increased with CCT, this was not counter to our hypothesis, since uneventful recovery is a composite outcome relying on the lack of several postoperative events, most of which are not dependent on myocardial function. In patients without circulatory arrest, CCT was not a predictor of change in LVEF but was a predictor of change in RVSF; interestingly, change in RVSF improves with CCT in this group rather than decline, and thus does not contradict our hypothesis. Overall, the described method of dosing DN cardioplegia appears safe for myocardial protection during ischemic periods of up to 5 hours.

Our DN dosing strategy starts with a single administration of cardioplegia for the first 90 minutes of CCT, followed by subsequent doses every 30 minutes. While maintaining the clinical utility of DN with 90 uninterrupted minutes of crossclamp time, the transition to reverse ratio 4:1 blood:DN crystalloid in maintenance doses may reduce potential cardiotoxic effects that can be a concern when using multiple concentrated doses of DN for prolonged crossclamp time. This reconciles the conceptual difficulties of the redosing strategies of previous studies. Lenoir and colleagues[11] speculated that the extended periods of time in between doses, one of the perceived advantages of DN cardioplegia due to its time-saving effect, allowed for disappearance of the protective components and cooling temperatures of cardioplegia, resulting in the elevated biomarkers found in their DN subgroup; previous literature[15] implying that more frequent doses of lidocaine-based cardioplegia (such as DN) may cause harmful negative inotropic effects prevented their surgeons from applying DN more frequently.

Our use of reverse ratio 4:1 blood:DN crystalloid in maintenance doses decreases the amount of crystalloid the patient receives and dilutes the lidocaine concentration, reducing its cardiotoxic potential. The reverse ratio also dilutes the potassium concentration to one more similar to the "low potassium" composition of conventional cardioplegia. Therefore, once the reverse ratio is introduced, succeeding

doses follow a redosing timing more similar to conventional cardioplegia. Maintenance doses are started at 90 minutes after the induction dose, with a retrograde coronary sinus dose every 30 minutes and an antegrade dose to right coronary artery every 60 minutes. Since the induction dose is sufficient for 90 minutes and following doses are administered every 30 minutes, there is still a time-saving benefit compared with whole-blood cardioplegia, which is redosed every 15 to 20 minutes after the induction dose.

Study Limitations

This is a single-center, single-surgeon retrospective study which may introduce bias and limit generalizability to other surgeons or institutions. In addition, the lack of a comparison group does not allow for direct analysis against other cardioplegic myocardial protection methods. However, we believe that the descriptive data of our unique redosing strategy provides an important preliminary data and insights in understanding the utility of this cardioplegic solution in aortic surgery. While surgeons at our institution have used this strategy for other adult cardiac operations with satisfactory outcomes, we urge caution on generalizing these findings to all of adult cardiac surgery. This study relies on echocardiographic parameters of cardiac function, LVEF and RVSF, to assess the safety and effectiveness of this redosing strategy in myocardial protection. RVSF is calculated by visual assessment, which is somewhat supported by echocardiography guidelines but not yet fully standardized.[26] This did not permit complex or nuanced assessment of RVSF but nonetheless provided a reasonably reliable assessment of global RV function. While we believe the values obtained from the standardized reports, we did not have access to a core laboratory for standardized review. Although the majority of patients had TTE reports both pre- and postoperatively, preoperative TEE data were used 16% of the time and postoperative TEE data was used 3% of the time. Although TEE data might have been confounded by other clinical factors, such as general anesthesia or pharmacologic support, we believe this bias is stronger in postoperative TEE, which was used less often, as 97% of patients had a discharge TTE on file. Additional analysis calculated solely by TEE values shows no relationship between CCT and primary outcomes (Figure E5). Lastly, while we were able to analyze clinical outcomes, we did not have data for cardiac biomarkers such as troponins, which would have added another dimension to our analysis of myocardial protection.

CONCLUSIONS

There is still uncertainty about the safety of DN cardioplegia in operations with prolonged myocardial ischemic time and no established method on how to redose. This paper describes a novel perfusion method of DN cardioplegia and its outcomes for diverse aortic operations with crossclamp times up to 287 minutes, including 72 operations with crossclamp times exceeding 180 minutes. This paper introduces the concept of "reverse ratio" DN cardioplegia, which consists of a lower concentration of lidocaine appropriate for redosing every 30 minutes. Our study found no relationship between crossclamp time and change in ventricular systolic function, postoperative cardiovascular support, or in-hospital mortality, suggesting that this redosing method may provide sufficient myocardial protection, even in prolonged cardiac ischemic periods. This paper also took the unique opportunity to study a cohort of patients with isolated aortic disease undergoing prolonged cardiopulmonary bypass; this subgroup also showed no relationship between crossclamp time and clinical outcomes. Future studies on biomarkers such as troponin could elucidate the effects and validate the use of "reverse ratio" DN cardioplegia in prolonged clamp times.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: aorta, cardioplegia, del Nido, myocardial ischemia, crossclamp, aortic surgery

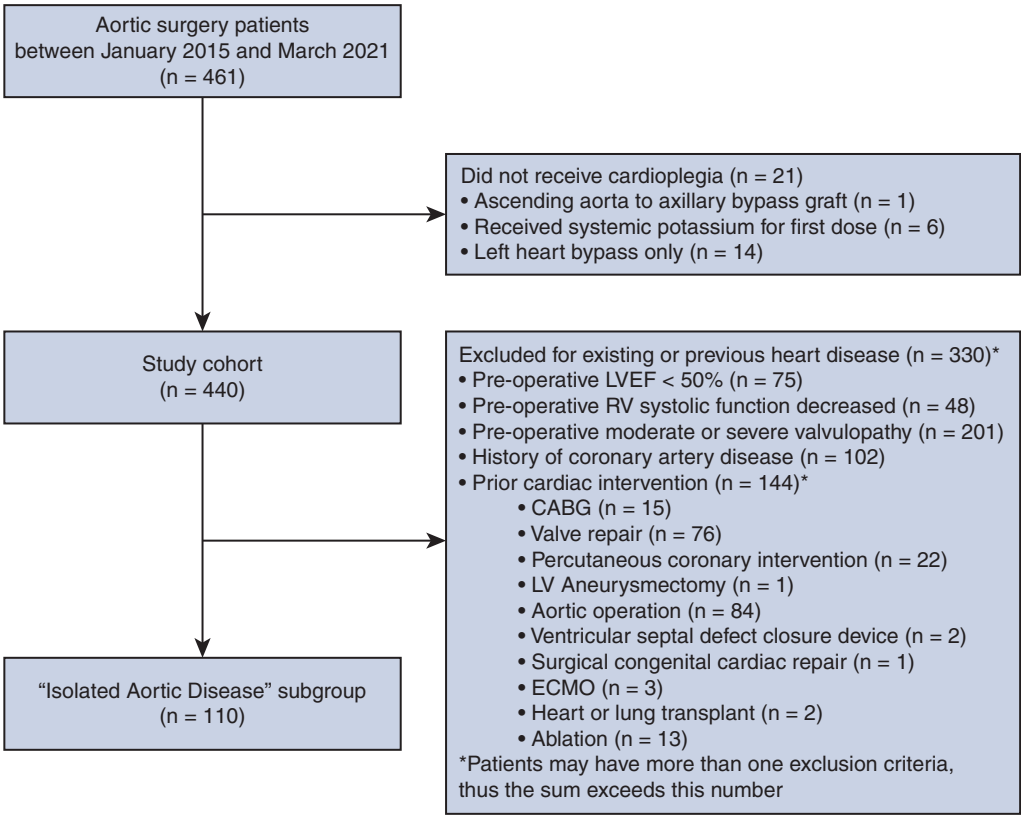

FIGURE E1. Consort diagram presenting exclusion criteria for the whole cohort of 440 patients and the isolated aortic disease subgroup of 110 patients. *LVEF*, Left ventricular ejection fraction; *RV*, right ventricle; *CABG*, coronary artery bypass graft; *LV*, left ventricular; *ECMO*, extracorporeal membrane oxygenation.

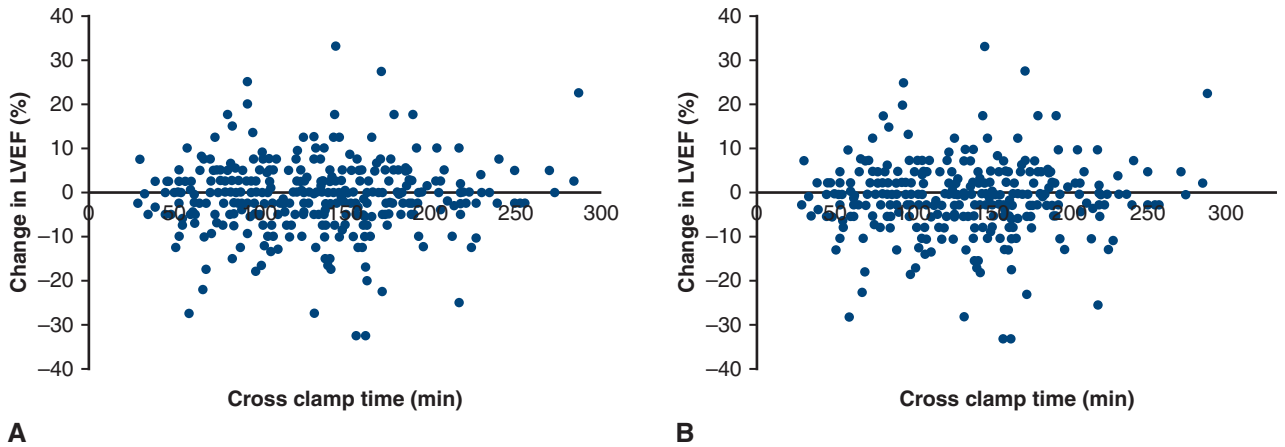

FIGURE E2. Change in LVEF by crossclamp time in aortic surgery patients that using the described del Nido dosing strategy after excluding patients with preoperative aortic insufficiency (A) or aortic stenosis (B) and subsequent aortic valve operation. On multivariable analysis, cross clamp time was not found to be a predictor for change in LVEF in the group without patients with corrected aortic insufficiency (coefficient estimate = 0.002; 95% CI, 0.988-1.016; $P = .814$) or corrected aortic stenosis (coefficient estimate = 0.004; 95% CI, 0.990-1.019; $P = .566$). *LVEF*, Left ventricular ejection fraction; *CI*, confidence interval.

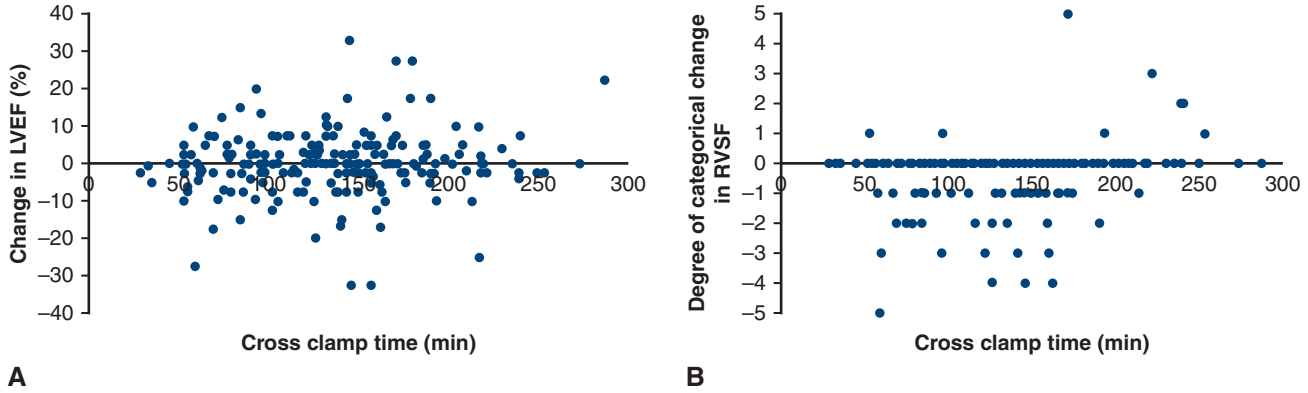

FIGURE E3. Change in LVEF (A) and change in RVSF (B) by crossclamp time in aortic surgery patients using the described del Nido dosing strategy but who did not undergo circulatory arrest. On multivariable analysis, crossclamp time was not found to be a predictor for change in LVEF (coefficient estimate = 0.017; 95% CI, 0.996-1.039; $P = .119$) but was a positively correlated with change in RVSF (coefficient estimate = 0.004; 95% CI, 1.001-1.007; $P = .004$). *LVEF*, Left ventricular ejection fraction; *RVSF*, right ventricular systolic function; *CI*, confidence interval.

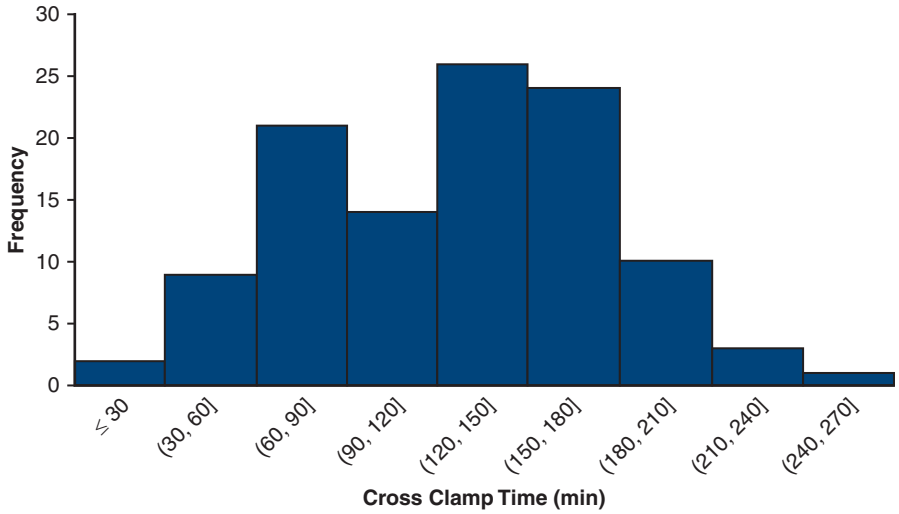

FIGURE E4. Distribution of crossclamp times of the 110 aortic surgery patients receiving del Nido cardioplegia in the isolated aortic disease subgroup.

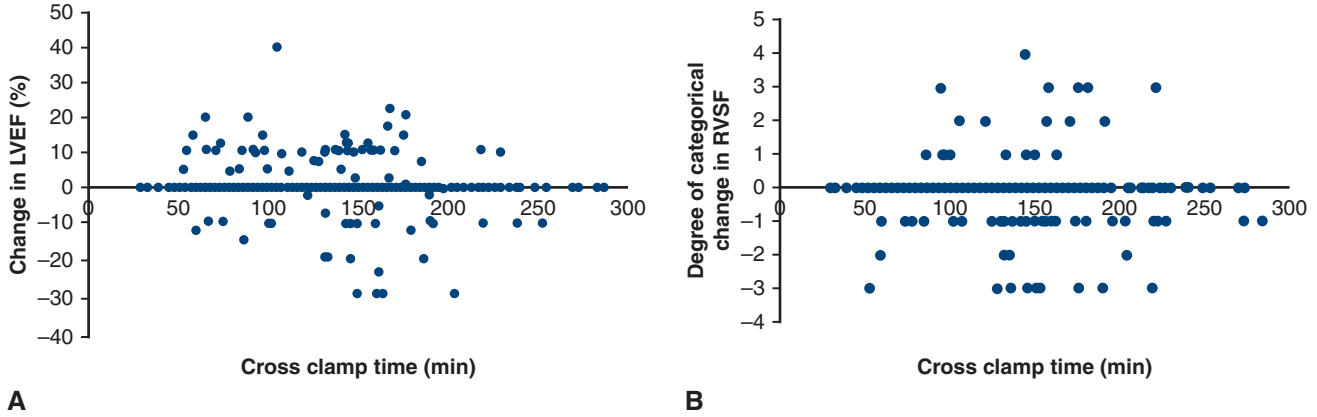

FIGURE E5. Change in LVEF (A) and change in RVSF (B) by crossclamp time in aortic surgery patients that using the described del Nido dosing strategy based on TEE data. On multivariable analysis, cross clamp time was not found to be a predictor for change in LVEF (coefficient estimate = –0.017; 95% CI, 0.999-1.001; $P = .951$) but or change in RVSF (coefficient estimate = 0.000; 95% CI, 0.999-1.000; $P = .745$). *LVEF*, Left ventricular ejection fraction; *RVSF*, right ventricular systolic function; *CI*, confidence interval.

TABLE E1. Composition of del Nido cardioplegia in standard and reverse ratio

Cardioplegia component	Conventional cardioplegia	Del Nido cardioplegia standard ratio 1:4 blood:crystalloid	Del Nido cardioplegia "reverse ratio" 4:1 blood:crystalloid
K, mmol/L	23.5	20.55	8.139
Mg, mmol/L	0.66	6.33	2.198
Ca, mmol/L	1.8	0.450	1.800
Lidocaine, mmol/L	0	0.420	0.104

Calculations used the following blood electrolyte levels: potassium 4.0 mmol/L, magnesium 2.0 mg/dL, calcium 9.0 mg/dL. *K*, Potassium; *Mg*, magnesium; *Ca*, calcium.

TABLE E2. Echocardiography data, n = 440

Echocardiography	LVEF, n (%)	RVSF, n (%)
Preoperative TTE or TEE	436 (99)	417 (95)
Preoperative TTE	361 (82)	333 (76)
Preoperative TEE	432 (98)	356 (81)
Postoperative TTE or TEE	436 (99)	421 (96)
Discharge TTE	412 (94)	376 (85)
Postoperative TEE	420 (95)	361 (82)
Both preoperative and postoperative echocardiography	432 (98)	398 (90)

LVEF, Left ventricular ejection fraction; *RVSF*, right ventricular systolic function; *TTE*, transthoracic echocardiogram; *TEE*, transesophageal echocardiogram.

TABLE E3. Sensitivity analysis for patients missing LVEF data

Variable	LVEF data (n = 432), N (%), median [IQR]	Missing LVEF data (n = 8), N (%), median [IQR]	*P* value
Preoperative characteristics			
Age	61 [50-69]	60 [56-78]	.297
Female	98 (23)	2 (25)	1.000
Body surface area	2.04 [1.88-2.20]	2.12 [1.93-2.23]	.636
Hypertension	319 (74)	6 (75)	1.000
On dialysis	5 (1)	0 (0)	1.000
Diabetes	60 (14)	1 (13)	1.000
Infective endocarditis	24 (6)	1 (13)	.944
Chronic lung disease	54 (13)	3 (38)	.120
Cerebrovascular disease	50 (12)	0 (0)	.646
Peripheral vascular disease	102 (24)	1 (13)	.753
Preoperative LVEF	60 [55-62]	33 [33-55]*	.067
Moderate or severe aortic stenosis	60 (14)	1 (13)	1.000
Moderate or severe aortic insufficiency	116 (27)	3 (38)	.787
Primary indication			
Aneurysm	285 (66)	3 (38)	.193
Dissection	102 (24)	4 (50)	.189
Valvular	28 (7)	0 (0)	.989
Obstruction	2 (1)	0 (0)	1.000
Infection	10 (2)	1 (13)	.493
Hematoma	6 (1)	0 (0)	1.000
Urgent or emergent status	211 (49)	3 (38)	.780
Operative details			
Ascending only	12 (3)	0 (0)	1.000
Proximal extension	204 (47)	1 (13)	.111
VSRR	84 (19)	0 (0)	.351
Bentall	82 (19)	0 (0)	.364
AV procedure	38 (9)	1 (13)	1.000
Distal extension	94 (22)	4 (50)	.141
Hemiarch replacement	20 (5)	2 (25)	.072
Partial/total arch replacement	74 (17)	2 (25)	.911
Proximal + distal extensions	122 (28)	3 (38)	**.857**
Root + hemiarch	17 (4)	(0)	1.000
Root + partial/total arch	23 (5)	0 (0)	1.000
AVR + hemiarch	42 (10)	3 (38)	.048†
AVR + partial/total arch	40 (9)	0 (0)	.778
Additional procedures			
CABG	76 (18)	2 (25)	.939
Mitral valve	29 (7)	1 (13)	1.000
Tricuspid valve	9 (2)	0 (0)	1.000
CPB time, min	180 [143-216]	219 [131-249]	.372
Crossclamp time, min	135 [93-164]	108 [91-155]	.541
Use of circulatory arrest	219 (50)	3 (38)	.731
Postoperative outcomes			
Inotropes on ICU admission	329 (76)	6 (75)	1.000
VIS on ICU admission	4.92 [1.05-9.67]	10.73 [7.33-13.16]	.191
Length of ICU stay, d	3.0 [1.6-6.0]	8.9 [4.7-9.7]	.014†
Length of hospital stay, d	8 [6-14]	11 [10-16]	.182
Uneventful recovery	274 (63)	2 (25)	.063
In-hospital mortality	9 (2)	2 (25)	.003†
Reexploration for bleed	21 (5)	1 (13)	.870
Pacemaker implantation	29 (7)	1 (13)	1.000
Respiratory failure	122 (28)	6 (75)	.013†

(Continued)

TABLE E3. Continued

Variable	LVEF data (n = 432), N (%), median [IQR]	Missing LVEF data (n = 8), N (%), median [IQR]	*P* value
Stroke	23 (5)	3 (38)	.002†
Acute renal failure	26 (6)	1 (13)	.989
Deep sternal infection	4 (1)	0 (0)	1.000
Postcardiotomy shock	14 (3)	1 (13)	.655

LVEF, Left ventricular ejection fraction; *IQR*, interquartile range; *VSRR*, valve-sparing root replacement; *AV*, aortic valve; *AVR*, aortic valve replacement; *CABG*, coronary artery bypass graft; *CPB*, cardiopulmonary bypass time; *ICU*, intensive care unit; *VIS*, vasoactive inotropic score. *n = 5 (63%). †*P* value < .05.

TABLE E4. Sensitivity analysis for patients missing RVSF data

Variable	RVSF data (n = 398), N (%), median [IQR]	Missing RVSF data (n = 42), N (%), median [IQR]	*P* value
Preoperative characteristics			
Age	60 [50-69]	63 [56-70]	.135
Female	87 (22)	13 (31)	.253
Body surface area	2.04 [1.87-2.20]	2.06 [1.95-2.29]	.429
Hypertension	291 (73)	34 (81)	.360
On dialysis	4 (1)	1 (2)	.972
Diabetes	54 (14)	7 (17)	.751
Infective endocarditis	23 (6)	2 (5)	1.000
Chronic lung disease	49 (12)	8 (19)	.320
Cerebrovascular disease	46 (12)	4 (10)	.889
Peripheral vascular disease	93 (23)	10 (24)	.677
Preoperative LVEF	59 [55-62]	60 [56-63]	.523
Moderate or severe aortic stenosis	56 (14)	5 (12)	.880
Moderate or severe aortic insufficiency	106 (26)	13 (31)	.677
Primary indication			
Aneurysm	263 (66)	25 (60)	.497
Dissection	94 (24)	12 (29)	.600
Valvular	25 (6)	3 (7)	1.000
Obstruction	2 (1)	0 (0)	1.000
Infection	9 (2)	2 (5)	.640
Hematoma	5 (1)	1 (2)	1.000
Urgent or emergent status	192 (48)	22 (52)	.728
Operative details			
Ascending only	10 (3)	2 (5)	**.724**
Proximal extension	185 (47)	20 (48)	**1.000**
VSRR	75 (19)	9 (21)	.842
Bentall	75 (19)	7 (17)	.892
AV procedure	35 (9)	4 (10)	1.000
Distal extension	86 (22)	12 (29)	**.403**
Hemiarch replacement	17 (4)	5 (12)	.074
Partial/total arch replacement	69 (17)	7 (17)	1.000
Proximal + distal extensions	117 (29)	8 (19)	**.217**
Root + hemiarch	16 (4)	1 (2)	.918
Root + partial/total arch	23 (6)	0 (0)	.217
AVR + hemiarch	40 (10)	5 (12)	.913
AVR + partial/total arch	38 (10)	2 (5)	.457
Additional procedures			
CABG	69 (17)	9 (21)	.654
Mitral valve	25 (6)	5 (12)	.292
Tricuspid valve	8 (2)	1 (2)	1.000
CPB time, min	181 [141-216]	180 [144-216]	.952
Crossclamp time, min	135 [93-164]	131 [97-166]	.998
Use of circulatory arrest	197 (50)	22 (52)	.847
Postoperative outcomes			
Inotropes on ICU admission	299 (75)	36 (86)	.180
VIS on ICU admission	4.58 [1.00-9.67]	7.66 [2.29-11.84]	.109
Length of ICU stay, d	3.0 [1.6-6.0]	5.0 [2.0-8.4]	.113
Length of hospital stay, d	8 [6-14]	10 [7-14]	.181
Uneventful recovery	253 (64)	23 (55)	.340
In-hospital mortality	8 (2)	3 (7)	.132
Re-exploration for bleed	19 (5)	3 (7)	.766
Pacemaker implantation	25 (6)	5 (12)	.292
Respiratory failure	112 (28)	16 (38)	.241

(Continued)

TABLE E4. Continued

Variable	RVSF data (n = 398), N (%), median [IQR]	Missing RVSF data (n = 42), N (%), median [IQR]	*P* value
Stroke	22 (6)	4 (10)	.484
Acute renal failure	21 (5)	6 (14)	.048*
Deep sternal infection	4 (1)	0 (0)	1.000
Postcardiotomy shock	11 (3)	4 (10)	.064
Change in LVEF (%)	0.0 [−5.0 to 2.5]	0 [−5.0 to 5.0]†	.906

RVSF, Right ventricular systolic function; *IQR*, interquartile range; *LVEF*, left ventricular ejection fraction; *VSRR*, valve-sparing root replacement; *AV*, aortic valve; *AVR*, aortic valve replacement; *CABG*, coronary artery bypass graft; *CPB*, cardiopulmonary bypass time; *ICU*, intensive care unit; *VIS*, vasoactive inotropic score. *P value < .05. †n = 36 (86%).

TABLE E5. Missing data, n = 440

Variable	Missingness (%)
BSA	1 (0.0)
Last hematocrit	8 (1.8)
Change in LVEF	8 (1.8)
Preoperative LVEF	4 (0.9)
Postoperative LVEF	4 (0.9)
Change in RVSF	42 (9.5)
Preoperative RVSF	23 (5.2)
Postoperative RVSF	19 (4.3)
VIS	5 (1.1)

BSA, Body surface area; *LVEF*, left ventricular ejection fraction; *RVSF*, right ventricular systolic function; *VIS*, vasoactive inotropic score.

TABLE E6. Multivariable analysis for predictors of continuous outcomes

Variable	Coefficient estimate	95% CI	*P* value
Change in LVEF			
Crossclamp time	0.001	−0.013, 0.015	.879
Preoperative LVEF	−0.339	−0.423 to –0.255	<.001*
Chronic lung disease	−4.937	−7.123 to –2.750	<.001*
Change in RVSF			
Crossclamp time	0.001	−0.001 to 0.003	.204
Preoperative RVSF	−0.676	−0.814 to –0.538	<.001*
Female	0.308	0.073-0.543	.011*
Diabetes	0.184	−0.084 to 0.452	.179
Urgent or emergent status	0.212	0.029-0.396	.024*
VIS			
Crossclamp time	−0.016	−0.041 to 0.008	.195
Age	0.061	0.007-0.116	.029*
Preoperative LVEF	−0.104	−0.187 to -0.020	.016*
Cerebrovascular disease	0.245	−2.224 to 2.714	.846
Chronic lung disease	2.596	0.319-4.873	.026*
History of endocarditis	2.797	−0.709 to 6.304	.119
Indication of dissection	1.252	−0.802 to 3.306	.233
Cardiopulmonary bypass time	0.039	0.019-0.059	.000*
Urgent or emergent status	0.165	−1.333 to 1.663	.829

CI, Confidence interval; *LVEF*, left ventricular ejection fraction; *RVSF*, right ventricular systolic function; *VIS*, vasoactive inotropic score. **P* value < .05.

TABLE E7. Multivariable analysis for predictors of binary outcomes

Variable	Odds ratio	95% CI	*P* value
Uneventful recovery			
Crossclamp time	0.993	0.988-0.997	.002*
Age	0.976	0.959-0.992	.004*
Preoperative LVEF	1.035	1.010-1.060	.004*
Cerebrovascular disease	0.589	0.298-1.162	.127*
Chronic lung disease	0.652	0.343-1.237	.191
History of endocarditis	0.259	0.094-0.707	.008*
Indication of dissection	0.262	0.160-0.428	<.001*
Urgent or emergent status	0.945	0.612-1.458	.798
In-hospital mortality			
Crossclamp time	0.991	0.977-1.006	.250
Age	1.033	0.981-1.089	.218
Preoperative LVEF	0.991	0.900-1.000	.051

CI, Confidence interval; *LVEF*, Left ventricular ejection fraction. **P* value < .05.

TABLE E8. Analysis of patients with postcardiotomy shock

Age	Sex	CPB time, min	CCT, min	Indication	Mechanical support	Outcome	Intra-/postoperative events
69	M	120	74	Type A	ECMO POD4	Mortality 6 months postoperative	None
80	M	151	116	Root aneurysm	Peripheral ECMO POD12	In-hospital mortality POD49	Postoperative tamponade and cardiac arrest
35	M	168	102	Type A	Central ECMO	d/c home	Coronary malperfusion due to aortic dissection, preoperative cardiac arrest, postoperative LVEF <10%
57	M	180	112	Aortic aneurysm	Ax/Fem ECMO	d/c acute rehab	Difficult reoperation after previous type A repair
59	M	218	180	Type A	Central ECMO	d/c to SNF POD44	Coronary malperfusion due to aortic dissection and rupture
78	M	222	135	Aortic aneurysm	Central ECMO	In-hospital mortality POD5 (stroke)	Reoperation of a zone 2 frozen elephant trunk
31	F	242	171	Type A	Femoral ECMO	d/c home	Coronary malperfusion due to aortic dissection, preoperative LVEF 10%
41	M	252	59	Aortic aneurysm	Central ECMO, central RVAD	In-hospital mortality POD1	Profound postbypass shock requiring ECMO, open abdomen and chest
46	M	265	217	Root aneurysm	Femoral ECMO	d/c to rehabilitation	Postoperative tamponade
65	M	307	181	Reoperation for root PSA	Ax/Fem ECMO	d/c to SAR	Prolonged CCT due to intractable bleeding
52	M	310	218	Prosthetic root abscess	Femoral ECMO	d/c home	Both coronary ostia involved in abscess cavity, requiring extensive reconstruction
56	M	341	219	Type A	Central ECMO	In-hospital mortality POD11	Coronary malperfusion due to type A, right and left coronary arteries were bypassed with SVGs off of ascending sidearm branches
66	M	378	146	Thoracic aorta rupture	Central ECMO	d/c home	Prolonged CCT due to aortic rupture

(Continued)

TABLE E8. Continued

Age	Sex	CPB time, min	CCT, min	Indication	Mechanical support	Outcome	Intra-/postoperative events
38	M	387	204	Reoperation for root PSA	Ax/Fem ECMO	d/c to SNF	Prolonged CCT due to need for extensive LVOT reconstruction
72	F	439	164	Type A	Central ECMO	d/c to rehabilitation	Coronary malperfusion due to aortic dissection, required left and right coronary bypasses

CPB, Cardiopulmonary bypass; *CCT*, crossclamp time; *M*, male; *ECMO*, extracorporeal membrane oxygenation; *POD*, postoperative day; *d/c*, discharged; *LVEF*, left ventricular ejection fraction; *Ax/Fem*, axillary artery and femoral vein; *SNF*, skilled nursing facility; *F*, female; *RVAD*, right ventricular assist device; *PSA*, pseudoaneurysm; *SVG*, saphenous vein graft; *LVOT*, left ventricular outflow tract.

TABLE E9. Patient characteristics for isolated aortic disease cohort

Variable	Isolated aortic disease (n = 110), N (%), median [IQR]	Remaining patients (n = 330), N (%), median [IQR]	*P* value
Preoperative characteristics			
Age	60 [50-68]	61 [51-70]	.367
Female	32 (29)	68 (21)	.088
Body surface area	2.07 [1.91-2.22]	2.03 [1.87-2.20]	.431
Hypertension	75 (68)	250 (76)	.150
On dialysis	1 (1)	4 (1)	1.000
Diabetes	12 (11)	49 (15)	.381
Infective endocarditis	0 (0)	25 (8)	.006*
Chronic lung disease	9 (8)	48 (15)	.119
Cerebrovascular disease	5 (5)	45 (14)	.015*
Peripheral vascular disease	23 (21)	80 (24)	.559
Primary indication			
Aneurysm	79 (72)	209 (63)	.132
Dissection	26 (24)	80 (24)	1.000
Valvular	3 (3)	25 (8)	.114
Obstruction	1 (1)	1 (0)	1.000
Infection	1 (1)	10 (3)	.378
Hematoma	2 (2)	4 (1)	1.000
Urgent or emergent status	54 (49)	160 (49)	1.000
Operative details			
Ascending only	1 (1)	11 (3)	.311
Proximal extension	48 (44)	157 (47)	.544
VSRR	35 (32)	49 (15)	<.001*
Bentall	11 (10)	71 (22)	.011*
AV procedure	2 (2)	37 (11)	.005*
Distal extension	34 (31)	64 (19)	.017*
Hemiarch replacement	9 (8)	13 (4)	.130
Partial/total arch replacement	25 (23)	51 (16)	.109
Proximal + distal extensions	27 (25)	98 (30)	.360
Root + hemiarch	9 (8)	8 (2)	.015*
Root + partial/total arch	9 (8)	14 (4)	.174
AVR + hemiarch	5 (5)	40 (12)	.037*
AVR + partial/total arch	4 (4)	36 (11)	.035*
CPB time, min	171 [143-197]	185 [141-226]	.030*
Crossclamp time, min	133 [86-165]	135 [95-164]	.335
Use of circulatory arrest	49 (45)	170 (52)	.248
Postoperative outcomes			
Inotropes on ICU admission	76 (69)	259 (79)	.061
VIS on ICU admission	3.14 [0-7.97]	5.24 [1.23-11.10]	.003*
Length of ICU stay, d	2.0 [1.3-5.0]	3.4 [1.8-6.8]	.006*
Length of hospital stay, d	7 [5-12]	9 [6-14]	.001*
Uneventful recovery	87 (79)	189 (57)	<.001*
In-hospital mortality	0 (0)	11 (3)	.113
Re-exploration for bleed	2 (2)	20 (6)	.130
Pacemaker implantation	2 (2)	28 (9)	.029*
Respiratory failure	18 (16)	110 (33)	.001*
Stroke	4 (4)	22 (7)	.350
Acute renal failure	3 (3)	24 (7)	.136
Deep sternal infection	1 (1)	3 (1)	1.000
Postcardiotomy shock	0 (0)	15 (5)	.049*
Change in LVEF (%)	0 [−2.5 to 2.5]	0 [−5 to 4.25]	.501
Decrease in RVSF	14 (14)	70 (24)	.054

IQR, Interquartile range; *VSRR*, valve-sparing root replacement; *AV*, aortic valve; *AVR*, aortic valve replacement; *CPB*, cardiopulmonary bypass time; *ICU*, intensive care unit; *VIS*, vasoactive inotropic score; *LVEF*, left ventricular ejection fraction; *RVSF*, right ventricular systolic function. *P value < .05.

TABLE E10. Outcomes of the isolated aortic disease subgroup

Variable	Crossclamp time coefficient estimate	95% CI	*P* value
Change in LVEF	−0.007	−0.026 to 0.012	.324
Change in RVSF	−0.001	−0.003 to 0.001	.234
VIS	−0.016	−0.071 to 0.039	.562
	Crossclamp time odds ratio	**95% CI**	***P* value**
Uneventful recovery	0.997	0.985-1.009	.662

CI, Confidence interval; *LVEF*, left ventricular ejection fraction; *RVSF*, right ventricular systolic function; *VIS*, vasoactive inotropic score.