J Extra Corpor Technol. 2020;52:173–81
The Journal of ExtraCorporeal Technology

Evaluating Changes in del Nido Cardioplegia Practices in Adult Cardiac Surgery

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Presented at the American Society of Extracorporeal Technology's 58th International Conference, St. Louis, Missouri, March 6–8, 2020.

Abstract: There has been a rapid adoption of the use of del Nido cardioplegia (DC) among adults undergoing cardiac surgery. We leveraged a multicenter database to evaluate differences over time in the choice and impact of cardioplegia type (DC vs. blood) among patients undergoing cardiac surgery. We evaluated 26,373 patients undergoing non-emergent coronary artery bypass and/or valve surgery between 2014–2015 (early period) and 2017–2018 (late period) at 31 centers. DC was compared with blood-based cardioplegia (BC: 1:1, 2:1, 4:1, 8:1, and variable ratio). We evaluated whether treatment choice differed across prespecified patient characteristics, procedure type, and perfusion practices by time period. We evaluated increased DC use with clinical outcomes (major morbidity and mortality, prolonged intubation, and renal failure), after adjusting for baseline characteristics, procedure type, center, and year. DC use increased from 19.6% in 2014–2015 to 41.5% in 2017–2018, $p < .001$. Increased DC use occurred among coronary artery bypass grafting (CABG), valve, and CABG + valve procedures, all $p < .001$. Differences in median procedural duration increased over time (DC vs. BC): 1) bypass duration was 11.0 minutes shorter with DC in the early period and 27.0 minutes shorter in the late period, and 2) cross-clamp duration was 7.0 minutes shorter with DC in the early period and 17.0 minutes shorter in the late period, all $p < .001$. There were no statistical differences in adjusted odds of major morbidity and mortality (odds ratio $[OR]_{adj}$: 1.01), prolonged intubation (OR_{adj}: .99), or renal failure (OR_{adj}: .80) by DC use ($p >$ .05). In this large multicenter experience, DC use increased over time and was associated with reduced bypass and ischemic time absent any significant differences in adjusted outcomes. **Keywords:** del Nido cardioplegia, coronary artery bypass grafts, CABG. *J Extra Corpor Technol. 2020;52:173–81*

Received for publication March 5, 2020; accepted July 16, 2020.
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Dr. Likosky receives funding from the Agency for Healthcare Research and Quality (R01HS026003 AHRQ) and the NHLBI (HL146619). The opinions expressed in this document are those of the authors and do not reflect the official position of the AHRQ, the NHLBI or the U.S. Department of Health and Human Services. Support for the MSTCVS Quality Collaborative is provided by the Blue Cross and Blue Shield of Michigan and Blue Care Network as part of the BCBSM Value Partnerships program.

INTRODUCTION

Most cardiac surgical operations are performed using cardioplegia to cause "elective reversible cardiac arrest" (1). Blood-based cardioplegia (BC), which involves variable blood-to-crystalloid ratios (e.g., 1:1, 2:1, 4:1, and 8:1), has been the most commonly used cardioplegia solution in adult coronary and/or valve surgery. Cardiac arrest is achieved by either antegrade and/or retrograde cardioplegia delivery and is readministered commonly every 15–20 minutes during the course of the cross-clamp period. These readministrations result in interruptions to the flow of an operation, as well as prolongation of the cross-clamp period with its associated adverse sequelae (2,3).

del Nido cardioplegia (DC), which has become a commonly used alternative to blood-based solutions within the pediatric cardiac surgery population (4,5), was developed as a single dose 1:4 blood-to-crystalloid cardioplegia component (4,5). This solution attenuates intracellular calcium concentration, contributing to increased myocardial depolarization and prolonged (greater than 1 hour) electrical quiescence (6). As a result, DC has become a dominant cardioplegia solution used in the pediatric population, given its proven safety and efficacy. Adoption of DC within an adult population has been influenced both by DC's theoretical benefits and equivalent outcomes when compared with BC in small series (7–9).

With this in mind, a large multicenter adult cardiac surgical database was leveraged to evaluate clinical outcomes associated with the increased application of DC among adult cardiac surgical operations.

MATERIALS AND METHODS

This study was deemed to be not regulated by the Institutional Review Board of the University of Michigan Health System (HUM00165575). There was no requirement for patient consent.

Patient Population

The Perfusion Measures and Outcomes (PERForm) registry, established in 2010 as a voluntary database, is organizationally structured within the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative (MSTCVS-QC). At the time of this publication, 42 hospitals contributed data to the PERForm registry, including 32 centers in and 10 centers outside of Michigan. Data from the PERForm registry are included as part of the MSTCVS-QC's quarterly meetings, which are focused on the review of processes and outcome data along with facilitation and evaluation of quality improvement studies.

Programs participating in the MSTCVS-QC use the Society of Thoracic Surgeons (STS) data collection form and submit data on a quarterly basis to both the STS database and the MSTCVS-QC data warehouse. The PERForm registry contains information related to the care and conduct of cardiovascular perfusion practices (a list of fields and definitions may be found at http://www.mstcvsqualitycollaborative.org/perform-registry). Each surgical record is merged with a record from the PERForm registry using a previously published algorithm (10). As part of its audit program, participating programs are subject to audits by the MSTCVS-QC for data validity and accuracy.

Patients older than or equal to 18 years operated on at one of 31 participating medical centers between 2014 and 2018 and underwent cardiac surgery using cardiopulmonary bypass (CPB) with cardioplegia were evaluated. The following exclusions were applied: 1) hospitals not submitting data to the PERForm registry continuously between 2014 and 2018, 2) missing values for the STS predicted risk of major morbidity or mortality, and 3) microplegia, crystalloid, crystalloid/custodial, or other cardioplegia solutions. Our final dataset included 26,373 patients from 26 hospitals.

Measures

The patients were divided into two groups based on the type of cardioplegia used: BC and DC. BC included the use of blood ratio (1:1, 2:1, 4:1, and 8:1) and variable ratio. Changes over time, both reporting practice and outcomes by year and between 2014 and 2018, were evaluated. In addition, analyses also involved comparisons of patient demographics and disease characteristics, intra- and post-operative practices, and outcomes between two time periods: 2014–2015 (early period, $n = 10{,}337$) and 2017–2018 (late period, $n = 10{,}700$).

A number of outcomes were evaluated, including post-surgical length of stay, prolonged intubation greater than 24 hours, return to CPB, acute kidney injury, use of an intra-aortic balloon pump (IABP), red blood cell transfusion (intra- and/or postoperative), and discharge location.

Statistical Analyses

Categorical variables were presented as n (%), and continuous variables were presented as median [25th, 75th percentile] in univariate analyses. Chi-square tests and Fisher exact tests were used to test the statistical significance for categorical variables, whereas Kruskal–Wallis and Wilcoxon rank-sum tests were used to test the statistical significance for continuous variables for multiple or two groups' comparison, as appropriate.

Generalized linear mixed-effect models were used to obtain adjusted odds ratio (OR) of DC use for outcomes such as STS major morbidity and mortality, prolonged intubation, and renal failure, adjusting for center as a random intercept, and for risk factors such as fixed effects including surgical year, age, gender, procedure type,

Table 1. Relative and absolute changes in study population characteristics (2014–2018).

	Year of Procedure						Absolute Change	Relative Change (%)
	2014	2015	2016	2017	2018	*p* Value	2018 vs. 2014	
Procedure count	4,742	5,595	5,336	5,487	5,213		471	9.9
Procedure: 8 categories (%Y)						<.001		
CABG	63.5	65.6	66.3	67.6	67.9		4.4	6.9
MVR + CABG	1.4	1.2	1.2	1.2	1.1		−.3	−21.4
AVR + CABG	9.5	9.3	8.8	7.9	7.8		−1.7	−17.9
MVR	3.2	3.0	3.2	3.5	3.9		.7	21.9
MVr	4.6	4.4	4.8	6.0	6.5		1.9	41.3
AVR	14.4	13.5	13.5	11.9	10.7		−3.7	−25.7
AVR + MVR	.1	.0	.0	.0	.0		−.1	−100.0
MVr + CABG	3.1	2.9	2.3	1.9	2.2		−.9	−29.0
Procedure: 3 categories (%Y)						<.001		
CABG	63.5	65.6	66.3	67.6	67.9		4.4	6.9
Valve	22.5	20.9	21.4	21.4	21.1		−1.4	−6.2
CABG + valve	14.0	13.5	12.3	11.0	11.0		−3.0	−21.4
Cardioplegia solution (%Y)								
del Nido (%Y)	13.9	24.5	28.4	37.8	45.3	<.0001	31.4	225.9
del Nido (among CABG)	13.5	22.7	27.3	35.4	44.2	<.0001	30.7	227.4
del Nido (among valve)	15.4	29.2	30.1	43.5	49.9	<.0001	34.5	224.0
del Nido (among CABG + valve)	13.4	25.7	31.1	41.3	43.6	<.0001	30.2	225.4
BC solution (%Y)						<.001		
1:1	.0	.0	.0	.0	.0		.0	NA
2:1	11.5	14.3	9.9	2.0	1.1		−10.4	−90.4
4:1	30.3	23.6	25.7	25.9	25.5		−4.8	−15.8
8:1	22.2	20.6	20.0	18.7	14.3		−7.9	−35.6
Variable ratio	22.1	17.0	16.0	15.6	13.7		−8.4	−38.0
Demographics								
Age (years), median	66.0	66.0	66.0	67.0	66.0	.13	.0	.0
Female (%Y)	29.6	29.5	28.0	28.1	28.1	.157	−1.5	−5.1
BSA (m^2), median	2.0	2.0	2.1	2.1	2.1	<.001	.0	1.0
Risk factors								
Diabetes mellitus (%Y)	41.8	43.5	44.7	42.9	43.3	.054	1.5	3.6
Vascular disease (%Y)	12.3	13.7	14.6	14.2	13.9	.094	1.6	13.0
Hematocrit (%Y)						<.001		
<36	27.8	25.1	24.8	23.7	21.5		−6.3	−22.7
36–39	26.7	25.4	24.4	25.5	26.4		−.3	−1.1
40–42	22.4	24.1	25.2	24.7	24.7		2.3	10.3
43+	23.1	25.4	25.6	26.1	27.4		4.3	18.6
LVEF% (%Y)								
<40	14.3	13.1	13.1	11.8	10.8	<.001	−3.5	−24.5
40–49	19.3	17.0	16.5	16.8	15.7	–	−3.6	−18.7
50–59	28.1	28.6	28.1	29.9	30.0		1.9	6.8
60+	38.4	41.3	42.3	41.5	43.4		5.0	13.0
Urgent (%Y)	46.9	48.0	48.0	47.9	48.1	.73	1.2	2.6
First time CV procedure (%Y)	94.5	95.3	95.7	96.2	96.1	<.001	1.6	1.7
Intraoperative care								
Lowest hematocrit on CPB, median	25.0	25.0	25.0	25.0	25.0	<.0001	.0	.0
CPB duration (min), median	103.0	101.0	101.0	103.0	104.0	<.001	1.0	1.0
Cross-clamp (XClamp) duration (min), median	78.0	78.0	78.0	79.0	81.0	<.001	3.0	3.8
Urine output on CPB per hour of CPB (mL/h), median	1.95	2.03	1.78	1.8	1.94	<.001	−.01	−.5%
Cardioplegia approach								
Induction route						<.001		
Antegrade aortic root	63.8	63.9	72.6	74.4	78.7		14.9	23.4
Antegrade coronary sinus	2.8	2.6	2.8	2.3	1.7		−1.1	−39.3
Retrograde	33.4	33.6	24.6	23.4	19.6		−13.8	−41.3
Strategies to manage hemodilution								
Static volume per BSA (mL/m^2), median	516.24	516.98	508.01	474.27	466.04	<.001	−50.2	−9.7
RAP (%Y)						<.001		
No RAP	22.5	17.8	15.7	17.2	14.6		−7.9	−35.1
<500 mL	28.2	29.5	30.8	36.6	40.3		12.1	42.9
500–699 mL	26.4	28.8	30.1	25.3	24.2		−2.2	−8.3
700 mL+	23.0	23.9	23.4	20.8	20.9		−2.1	−9.1

Table 1. Continued.

	Year of Procedure						Absolute Change	Relative Change (%)
	2014	2015	2016	2017	2018	*p* Value	2018 vs. 2014	
Net prime volume (%Y)						<.001		
<500 mL	16.4	19.4	23.9	25.6	26.1		9.7	59.1
500–999 mL	53.2	56.9	54.3	56.2	27.7		−25.5	−47.9
1–1.4 L	25.8	20.7	19.0	16.4	13.6		−12.2	−47.3
1.5 L+	4.6	3.0	2.8	1.7	2.6		−2.0	−43.5
Blood management strategies								
Conventional ultrafiltration (%Y)	25.6	26.3	22.5	22.8	21.3	<.001	−4.3	−16.8
Total intraoperative ultrafiltration volume per kg (mL/kg)	8.0	8.6	8.0	8.2	8.0	.31	−.01	−.1
Cell salvage (%Y)	79.5	79.1	76.7	78.2	78.9	.006	−.6	−.8
Cell salvage volume (mL/m^2), median	500.0	500.0	500.0	500.0	450.0	<.001	−100.0	−18.2
ANH (%Y)						<.001		
No ANH	91.7	85.8	84.2	83.6	82.9		−8.8	−9.6
<400 mL	.2	1.3	2.9	4.1	5.3		5.1	2,550.0
400–799 mL	4.0	8.4	7.7	7.4	6.4		2.4	60.0
800 mL+	4.2	4.5	5.2	4.9	5.4		1.2	28.6
Cardiotomy suction (%Y)	74.5	65.8	71.5	67.8	74.4	−.1	−.1	−.1
Total cardioplegia volume per hour of cross-clamp (mL/h), median	1,739.1	1,600.0	1,518.1	1,490.1	1,457.1	<.001	−282.0	−16.2
Glucose management (mg/dL), median								
1st intraoperative	112.0	114.0	115.0	113.0	112.0	<.001	.0	.0
Last intraoperative	149.0	150.0	147.0	148.0	144.0	<.001	−5.0	−3.4
Highest intraoperative	183.0	181.0	176.0	172.0	169.0	<.001	−14.0	−7.7
Outcomes								
Postsurgical length of stay (days), median	6.0	6.0	6.0	6.0	6.0	<.001	.0	.0
Prolonged intubation (%Y)	8.3	8.9	7.9	8.1	8.1	.37	−.2	−2.4
Return to CPB (%Y)	2.9	2.8	3.0	2.5	3.4	.12	.5	17.2
Acute kidney injury (%Y)	23.6	23.1	22.7	22.5	21.1	.04	−2.5	−10.6
IABP (%Y)						.32		
No IABP	94.0	94.6	95.0	94.3	94.7		.7	.7
Preoperative	4.3	3.6	3.4	3.6	3.6		−.7	−16.3
Intraoperative	1.3	1.4	1.3	1.8	1.5		.2	15.4
Postoperative	.4	.3	.3	.4	.2		−.2	−50.0
Red blood cell transfusion (%Y)						<.001		
None	63.7	63.5	65.1	66.2	69.2		5.5	8.6
Intraoperative only	7.7	8.2	7.6	7.1	7.0		−.7	−9.1
Postoperative only	19.2	18.4	17.8	17.9	16.4		−2.8	−14.6
Intra- and postoperative	9.4	9.9	9.5	8.9	7.4		−2.0	−21.3
Discharge location (%Y)						<.001	−2.0	−21.3
Home	75.2	74.0	76.1	75.5	77.5		–	–
Transitional/rehabilitation	23.1	23.4	21.4	22.4	20.9		2.3	3.1
Death	1.3	2.0	1.6	1.6	1.4		−2.2	−9.5
Other	.3	.6	.9	1.2	1.7		1.4	466.7

MVR, mitral valve replacement; MVr, mitral valve repair; ANH, acute normovolemic hemodilution.

hypertension, atrial fibrillation, New York Heart Association class, estimated glomerular filtration rate (EGFR), left ventricular ejection fraction (LVEF), previous myocardial infarction (MI), diabetes, previous cardiac surgery, body mass index (BMI), and admission acuity. Interaction terms between use of DC and risk factors (ejection fraction, EGFR, admission acuity, and gender) were tested in the models, with major morbidity/mortality, prolonged intubation, and renal failure as dependent variables. Sensitivity analysis was performed in each procedure type. p values < .05 were considered statistically significant. Statistical analysis used R version 3.6.1.

RESULTS

Demographic and comorbidity comparisons across years are displayed in Table 1. Overall, coronary artery bypass grafting (CABG) procedures increased 4.4% between 2018 vs. 2014, whereas aortic valve replacement (AVR) decreased 3.7%. Use of DC increased 31.4%; choice of cardioplegia did not differ across procedure type (Figure 1).

Table 2 displays comparisons of BC and DC in both early (2014–2015) and late (2017–2018) time periods. In the early time period, the most common blood ratio was 4:1 (33.2% of procedures), followed by 8:1 (26.6%) and variable ratio

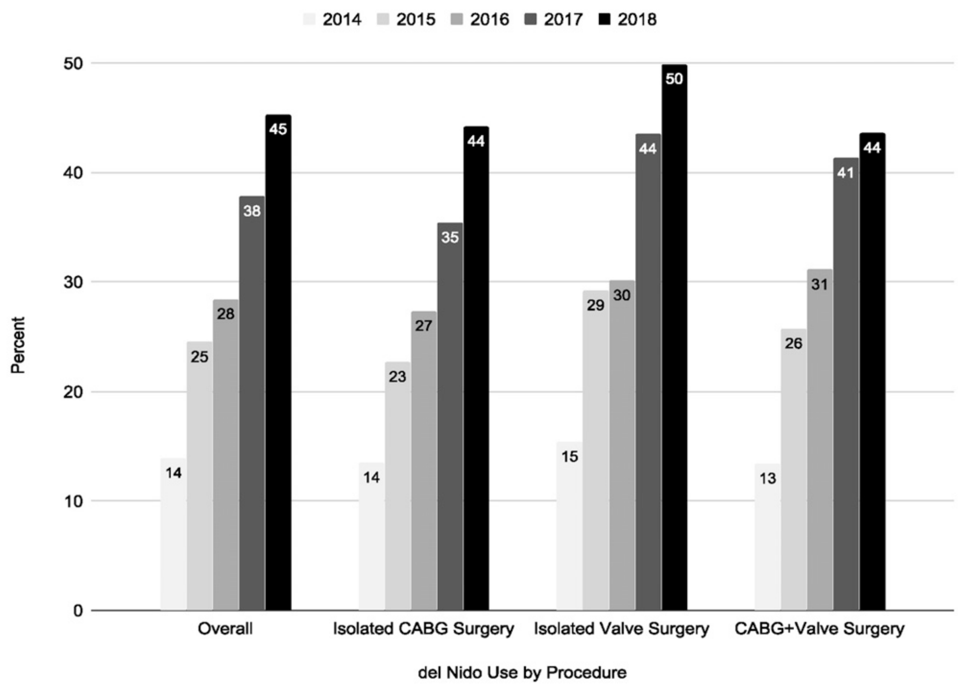

Figure 1. del Nido use over time by procedure.

(24.0%). In addition, DC use was 4.1% higher (BC: 20.8% vs. DC: 24.9%), was performed more often on patients with higher ejection fractions, more often delivered antegrade through the aortic root (59.3% vs. 82.8%), and was associated with higher median static prime volumes per body surface area (BSA) (510.7 mL/m^2 vs. 538.8 mL/m^2) and higher net prime volumes, more conventional ultrafiltration use (21.6% vs. 43.9%), cell salvage use (76.9% vs. 88.9%), and cardiotomy suction use (67.3% vs. 80.4%). Nonetheless, increased DC use over time was associated with qualitatively equivalent lowest hematocrit on CPB and clinical outcomes exclusive of lower red blood cell transfusions. By contrast, in the earlier time period, DC was associated with fewer urgent operations (48.6% vs. 42.9%), 11-minute shorter median CPB (104.0 minutes vs. 93.0 minutes) and 7-minute shorter cross-clamp (80.0 minutes vs. 73.0 minutes) durations, less use of retrograde autologous priming (RAP) volume less than 500 mL (31.1% vs. 19.7%), lower median total cardioplegia volume per hour of cross-clamp duration (154.6 min/h vs. 949.2 mL/kg), and lower median highest intraoperative glucose (187 mg/dL vs. 165.0 mg/dL).

These findings persisted in the later time period, with few exceptions. For instance, DC was used more commonly among urgent patients (46.6% vs. 50.0%) and was more commonly associated with retrograde autologous prime volume less than 500 mL (35.0% vs. 43.2%). On the other hand, DC was associated with 27-minute shorter median CPB (115.0 minutes vs. 88.0 minutes) and 17-minute shorter cross-clamp (87.0 minutes vs. 70.0 minutes) durations and less cell salvage use (85.6% vs. 68.6%). Median static prime volumes per BSA were not statistically different in the later time period (476.8 mL/m^2 vs. 465.8 mL/m^2).

In crude analysis, DC use was associated with a 23% reduced odds of prolonged intubation (OR: .77; 95% CI: .70–.85), a 26% reduced odds of renal failure (OR: .74; 95% CI: .62–.90), and a 17% reduced odds of major morbidity or mortality (OR: .83; 95% CI: .76–.90). After adjustment for baseline risk and year, DC use was associated with a 1% nonsignificant reduced odds of prolonged intubation (OR_{adj}: .99; 95% CI: .86–1.13), a 20% nonsignificant reduced odds of renal failure (OR_{adj}: .80; 95% CI: .63–1.01), and a 1% nonsignificant increased odds of major morbidity or mortality (OR_{adj}: 1.01; 95% CI: .90–1.13; Table 3). These findings were qualitatively similar across the type of procedure.

Next, we explored a number of interactions, all of which were nonsignificant ($p > .05$).

DISCUSSION

In this large, prospective, multi-institutional study, the relationship between changes in DC use and clinical outcomes following cardiac surgery was assessed. Between 2014 and 2018, DC use increased 31.4% (13.9% vs. 45.3%), a finding that was consistent across all procedure types. Differences in CPB and cross-clamp between DC and BC grew wider over time—DC use being associated with a shorter cross-clamp and CPB times than BC in both instances. In multivariable analysis, accounting for preoperative risk, the

Table 2. Study population characteristics by changes in cardioplegia type (2014–2018).

	2014–2015			Absolute Change	Relative Change (%)	2017–2018			Absolute Change	Relative Change (%)
	BC	DC	*p* Value	DC vs. BC		BC	DC	*p* Value	DC vs. BC	
Procedure Count	8,308	2,029		−6,279	−75.6	6,262	4,438		−1,824	−29.1
Procedure: 3 categories (%Y)			<.001					<.001		
Isolated CABG	65.5	61.1		−4.4	−6.7	69.8	64.8		−5.0	−7.2
CABG + valve	20.8	24.9		4.1	19.7	19.4	23.9		4.5	23.2
Isolated valve	13.7	13.9		.2	1.5	10.8	11.3		.5	4.6
Cardioplegia solution (%Y)										
1:1	.0	.0	–	–	–	–	.0	–	–	–
2:1	16.2	.0	–	–	–	–	2.7	–	–	–
4:1	33.2	.0	–	–	–	–	43.9	–	–	–
8:1	26.6	.0	–	–	–	–	28.3	–	–	–
Variable ratio	24.0	.0	–	–	–	–	25.1	–	–	–
del Nido		100.0	–	–	–	–	100.0	–	–	–
Demographics										
Age (years), median	66.0	66.0	.02	.0	.0	66.0	67.0	<.001	1.0	1.5
Female (%Y)	29.2	30.8	.18	1.6	5.5	27.6	28.8	.16	1.2	4.3
BSA (m^2), median	2.0	2.0	.55	.0	−.5	2.1	2.1	.62	.0	.0
Risk factors										
Diabetes mellitus (%Y)	43.0	41.4	.20	−1.6	−3.7	44.0	41.7	.02	−2.3	−5.2
Vascular disease (%Y)	13.5	11.2	.01	−2.3	−17.0	14.6	13.3	.07	−1.3	−8.9
Hematocrit (%Y)			.19					.03		
<36	26.4	25.9		−.5	−1.9	23.4	21.6		−1.8	−7.7
36–39	25.6	27.8		2.2	8.6	26.3	25.3		−1.0	−3.8
40–42	23.4	23.1		−.3	−1.3	24.3	25.2		.9	3.7
43+	24.6	23.2		−1.4	−5.7	26.0	27.9		1.9	7.3
LVEF% (%Y)			<.001					.00		
<40	14.3	12.9		−1.4	−9.8	12.5	11.4		−1.1	−8.8
40–49	13.2	11.9		−1.3	−9.8	13.5	11.5		−2.0	−14.8
50–59	31.7	27.4		−4.3	−13.6	31.7	31.7		.0	.0
60+	40.8	47.8		7.0	17.2	42.3	45.4		3.1	7.3
Urgent (%Y)	48.6	42.9	<.001	−5.7	−11.7	46.6	50.0	.001	3.4	7.3
First time CV procedure (%Y)	94.9	94.9	.99	.0	.0	96.2	96.1	.76	−.1	−.1
Intraoperative care										
Lowest hematocrit on CPB, median	25.0	24.5	.30	−.5	−2.0	25.8	25.0	<.0001	−.8	−3.1
CPB duration (min), median	104.0	93.0	<.001	−11.0	−10.6	115.0	88.0	<.001	−27.0	−23.5
Cross-clamp (XClamp) duration (min), median	80.0	73.0	<.001	−7.0	−8.8	87.0	70.0	<.001	−17.0	−19.5
Urine output on CPB per hour of CPB (mL/h), median	1.9	2.2	<.001	.3	14.5	1.8	1.9	.058	.1	3.3
Cardioplegia approach										
Induction route			<.001					<.001		
Antegrade aortic root	59.3	82.8		23.5	39.6	66.0	91.1		25.1	38.0
Antegrade coronary sinus	2.9	1.9		−1.0	−34.5	2.5	1.2		−1.3	−52.0
Retrograde	37.9	15.3		−22.6	−59.6	31.4	7.7		−23.7	−75.5
Strategies to manage hemodilution										
Static volume per BSA (mL/m^2), median	510.7	538.8	<.001	28.1	5.5	476.8	465.8	.06	−11.1	−2.3
RAP volume (%Y)			<.001					<.001		
No RAP	14.9	40.8		25.9	173.8	16.8	14.8		−2.0	−11.9
<500 mL	31.1	19.7		−11.4	−36.7	35.0	43.2		8.2	23.4
500–699 mL	29.5	20.2		−9.3	−31.5	21.6	29.2		7.6	35.2
700 mL+	24.5	19.3		−5.2	−21.2	26.6	12.7		−13.9	−52.3
Net prime volume (%Y)			<.001					<.001		
<500 mL	21.1	5.3		−15.8	−74.9	27.8	23.2		−4.6	−16.5
500–999 mL	56.4	50.3		−6.1	−10.8	51.9	64.1		12.2	23.5
1–1.4 L	18.7	40.9		22.2	118.7	17.4	11.7		−5.7	−32.8
1.5 L+	3.8	3.4		−.4	−10.5	3.0	1.1		−1.9	−63.3

Table 2. Continued.

	2014–2015			Absolute Change	Relative Change (%)	2017–2018			Absolute Change	Relative Change (%)
	BC	DC	*p* Value	DC vs. BC		BC	DC	*p* Value	DC vs. BC	
Blood management strategies										
Conventional ultrafiltration (%Y)	21.6	43.9	<.001	22.3	103.2	15.8	30.8	<.001	15.0	94.9
Total intraoperative ultrafiltration volume per kg (mL/kg)	7.59	9.41	<.001	1.82	24.0	7.04	8.59	<.001	1.55	22.0
Cell salvage (%Y)	76.9	88.9	<.001	12.0	15.6	85.6	68.6	<.001	−17.0	−19.9
Cell salvage volume (mL)	500.0	600.0	<.001	100.0	20.0	460.0	490.0	.01	30.0	6.5
ANH (%Y)			<.001					<.001		
No ANH	87.4	92.9		5.5	6.3	77.5	91.4		13.9	17.9
<400 mL	.9	.5		−.4	−44.4	6.9	1.6		−5.3	−76.8
400–799 mL	7.1	3.3		−3.8	−53.5	9.4	3.4		−6.0	−63.8
800 mL+	4.6	3.3		−1.3	−28.3	6.2	3.6		−2.6	−41.9
Cardiotomy suction (%Y)	67.3	80.4	<.001	13.1	19.5	64.9	79.3	<.001	14.4	22.2
Total cardioplegia volume per hour of cross-clamp (mL/h), median	1,854.6	949.2	<.001	−905.3	−48.8	1,854.2	1,043.5	<.001	−810.7	−43.7
Glucose management (mg/dL), median										
1st intraoperative	112.0	115.0	<.001	3.0	2.7	113.0	112.0	.002	−1.0	−.9
Last intraoperative	150.0	147.0	.007	−3.0	−2.0	148.0	143.0	<.001	−5.0	−3.4
Highest intraoperative	187.0	165.0	<.001	−22.0	−11.8	179.0	160.0	<.001	−19.0	−10.6
Outcomes										
Postsurgical length of stay (days), median	6.0	6.0	.81	.0	.0	6.0	6.0	<.001	.0	.0
Prolonged intubation (%Y)	9.2	6.2	<.001	−3.0	−32.6	8.8	7.2	.00	−1.6	−18.2
Return to CPB (%Y)	2.7	3.4	.11	.7	25.9	2.7	3.3	.12	.6	22.2
Acute kidney injury (%Y)	23.4	23.1	.78	−.3	−1.3	22.1	21.5	.48	−.6	−2.7
IABP (%Y)			.003					<.001		
No IABP	93.9	96.0		2.1	2.2	93.4	96.0	–	2.6	2.8
Preoperative	4.2	2.8		−1.4	−33.3	4.4	2.3		−2.1	−47.7
Intraoperative	1.5	1.1		−.4	−26.7	1.8	1.4		−.4	−22.2
Postoperative	.4	.1		−.3	−75.0	.3	.3		.0	.0
Red blood cell transfusion (%Y)			<.001					<.001		
None	62.9	66.3		3.4	5.4	65.6	70.5		4.9	7.5
Intraoperative only	7.5	10.0		2.5	33.3	7.0	7.2		.2	2.9
Postoperative only	19.6	15.6		−4.0	−20.4	18.4	15.4		−3.0	−16.3
Intra- and postoperative	10.1	8.1		−2.0	−19.8	9.1	6.9		−2.2	−24.2
Discharge location (%Y)			.91					<.001		
Home	74.5	74.9		.4	.5	74.4	79.3		4.9	6.6
Transitional/rehabilitation	23.3	23.2		−.1	−.4	23.6	18.9		−4.7	−19.9
Death	1.8	1.5		−.3	−16.7	1.6	1.4		−.2	−12.5
Other	.5	.4		−.1	−20.0	1.5	1.4		−.1	−6.7

hospital, and year, cardioplegia strategy was not independently associated with an increased odds of prolonged intubation, renal failure, or overall major morbidity or mortality.

A number of study limitations are worth noting. As with any observational study, unmeasured confounding (e.g., cardioplegia redosing and cardioplegia solutions) may persist. Nonetheless, standard statistical approaches (e.g., accounting for base patient risk, surgeon, and hospital) were used. Second, although the extent of myocardium protected during the CPB period was not assessed, the absence of this information is unlikely to bias the evaluation of changes in DC use over time. Last, findings from this study may only be generalizable to centers participating in the PERForm registry. Nonetheless, this study represents, to our knowledge, the largest multi-institutional study evaluating the relationship between DC use and outcomes within an adult cardiac surgery population.

Our findings, which confirm those of other smaller, often single institutional series, are that DC use may be safely performed within the setting of adult cardiac surgery. The longer depolarized period afforded by DC relative to BC permits less frequent cardioplegia redosing. Surgeons may additionally benefit with fewer associated workflow disruptions, allowing shorter ischemic durations (11). These strategic advantages, including its application within less invasive operations, may account for some of the increased utilization of DC over our study.

Findings from the current study further inform the relationship between DC use and intra- or postoperative sequelae. Prior investigators have reported conflicting findings

Table 3. Multivariable modeling results.

Characteristic	STS Major Morbidity and Mortality			Prolonged Intubation			Renal Failure		
	OR	2.5%	97.5%	OR	2.5%	97.5%	OR	2.5%	97.5%
Age	1.05	1.00	1.10	1.08	1.03	1.14	1.00	.90	1.11
del Nido (vs. blood)	1.01	.90	1.13	.99	.86	1.13	.80	.63	1.01
Gender (female vs. male)	1.17	1.08	1.27	1.29	1.16	1.42	.69	.56	.84
CABG (vs. valve)	.56	.50	.63	.47	.41	.54	.56	.44	.72
CABG + valve (vs. valve)	1.27	1.11	1.44	1.21	1.04	1.40	1.02	.78	1.34
Hypertension	1.09	.95	1.25	1.14	.97	1.36	1.74	1.17	2.57
Atrial fibrillation	1.79	1.65	1.94	1.89	1.72	2.08	2.56	2.15	3.04
New York Heart Association Class (III and IV)	1.52	1.37	1.68	1.63	1.44	1.83	1.60	1.30	1.98
EGFR									
≥90	Ref			Ref					
60–90	1.09	.97	1.21	1.08	.95	1.24	1.22	.91	1.63
30–60	1.62	1.43	1.83	1.45	1.25	1.68	3.39	2.52	4.56
15–30	4.54	3.57	5.77	2.30	1.71	3.09	26.40	18.35	37.97
<15	2.88	2.39	3.47	2.78	2.25	3.45	2.32	1.45	3.71
Ejection fraction									
<40	Ref			Ref					
40–50	.83	.73	.96	.80	.68	.94	1.12	.84	1.48
50–60	.69	.61	.78	.64	.56	.74	.84	.65	1.09
≥60	.62	.55	.70	.55	.48	.63	.69	.53	.90
Previous MI	1.13	1.04	1.24	1.22	1.09	1.36	.97	.80	1.18
Diabetes	1.19	1.10	1.29	1.17	1.06	1.29	1.51	1.26	1.82
Previous intervention	1.23	1.13	1.34	1.35	1.23	1.49	1.14	.96	1.37
BMI									
<31	Ref	–	–	Ref	–	–	–	–	–
31–37	1.12	1.02	1.23	1.22	1.10	1.37	1.20	.98	1.47
>37	1.37	1.22	1.54	1.51	1.32	1.73	1.72	1.36	2.17
Surgical year	.99	.96	1.02	.99	.96	1.03	1.01	.95	1.07

regarding DC's association with longer CPB and cross-clamp periods. Yerebakan and colleagues analyzed data from 88 patients undergoing CABG in the setting of a recent MI, of whom 40 received BC and 48 received DC (9). The authors propensity matched the two cohorts, with each reflecting a unique 1-year time period. Similar to our series, patients receiving BC had significantly greater average exposure to total cardioplegia volume (1,988 mL vs. 996 mL) as well as greater average additional doses of cardioplegia (3.2 vs. .2). There were no significant differences in the average number of packed red blood cell transfusions (1.4 vs. .9) or other evaluated in-hospital complications (e.g., permanent pacemaker, atrial fibrillation, acute renal failure, unplanned reoperation, postoperative inotropic support or IABP usage, and low cardiac output syndrome). Similar findings have been reported within a cohort of 240 patients undergoing isolated AVR (7). Sorabella analyzed data from a cohort of 113 patients (BC: 61 vs. DN: 52) undergoing reoperative isolated AVR (12). Although average CPB (BC: 67.2 vs. DC: 61.3) and cross-clamp durations (100.5 vs. 93.1) were statistically similar, the total cardioplegia delivery was higher for BC (1,985.4 mL vs. 1,147.6 mL; $p < .001$), and outcomes other than average hospital length of stay (10.1 days vs. 7.9 days; $p = .035$) were similar. Mick and colleagues reported on a cohort of 85 isolated aortic and 85 mitral valve operations performed at a single institution (13). Patients within each operation type were propensity matched by cardioplegia strategy. Within the aortic valve cohort, BC patients had longer CPB and cross-clamp durations, peak glucose values, and highest measured postoperative troponins. Nonetheless, other postoperative outcomes were statistically similar between the two cardioplegia groups. Within the mitral valve cohort, BC patients had similar CPB and cross-clamp durations and highest measured postoperative troponins, although BC patients had higher peak glucose values. Similar to the aortic valve patients, postoperative outcomes were statistically similar between the two cardioplegia groups. Last, in a recent single-center randomized trial of BC vs. DC among adult CABG and/or valve patients, Ad and colleagues observed nonsignificant differences in CPB duration (103 minutes vs. 97 minutes; $p = .288$) although shorter cross-clamp duration (83 minutes vs. 70 minutes; $p = .018$) with DC (11). Similar to the present series, Ad found no significant differences in STS-defined morbidity or mortality.

To our knowledge, our study is the first multicenter study to evaluate changes in DC practice and clinical outcomes. The absolute rate of increase of DC (2018 vs. 2014) was similar across procedure type (overall: 31.4%; isolated CABG: 30.7%; isolated valve: 34.5%; CABG + valve: 30.2%). Indeed, large-scale differences over time in patient presentation were not apparent (Table 1). Together, these findings suggest that DN adoption rates are predominantly independent of the surgical procedure, and instead may be driven by a surgeon's routine. Our current analysis suggests that surgeons were more likely to deliver DC induction doses through the antegrade aortic root route while more often using conventional ultrafiltration and less often using cell salvage in the later time period relative to BC. Despite higher crystalloid load with DC, intraoperative transfusion rates were qualitatively equivalent in 2017–2018 between DC and BC, as were median nadir hematocrit during CPB. Further work is necessary to understand how DN is implemented by surgeons, including redosing intervals and constitution of the DN solution.

In this large, multicenter experience, of more than 26,000 adult cardiac surgery patients, increased DC use was associated with equivalent outcomes relative to BC. Future studies should evaluate its use and benefit across distinct pathophysiologic presentations (e.g., acute ischemia) to support its application within patients at increased risk of harm.

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