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Original Article

Single-Shot Cold Histidine-Tryptophan-Ketoglutarate Cardioplegia for Long Aortic Cross-Clamping Durations in Neonates

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Objective: More than 30% of European pediatric cardiac surgery centers use single-dose cold histidine-tryptophan-ketoglutarate cardioplegia (Custodiol; Dr Franz Köhler Chemie GmbH, Bensheim, Germany). In neonates with transposition of the great arteries, arterial switch surgery (ASO) implies aortic division, and it is unknown whether repeated ostial cannulation causes intimal insult and affects long-term results, and therefore, single-dose Custodiol is appealing. The present study investigated the association among myocardial no-flow duration, postoperative troponins, and postoperative outcomes in neonates undergoing ASO with Custodiol cardioplegia.

Design: Retrospective analysis of the association among myocardial no-flow duration, postoperative troponin release (concentration magnitude × measurement duration within 48 h), and outcomes using stratification according to coronary anatomy and attending surgeon.

Setting: Single-institutional, tertiary pediatric cardiac surgery unit of a university hospital.

Participants: The study comprised 101 neonates undergoing ASO.

Interventions: None.

Measurements and Main Results: The mean age of patients was 6.1 ± 5.4 days, the cardiopulmonary bypass duration was 108.7 ± 54.1 minutes, the temperature during cross-clamping was 31.1°C ± 1.7°C, the duration of mechanical ventilation was 4 (3-6) days, the length of intensive care unit stay was 7 (5-8) days, delayed sternal closure occurred in 32 (31.7%) patients, and no patients died. The myocardial no-flow duration averaged 62.3 ± 14.6 minutes and was linked with both troponin release ($p = 0.04$) and low cardiac output syndrome, as assessed by the requirement for delayed sternal closure ($p = 0.03$), regardless of cardiopulmonary bypass duration and temperature. Eighty-two percent of the patients with myocardial no-flow duration >74 minutes necessitated delayed sternal closure.

Conclusions: Single-dose Custodiol may be inadequate for prolonged cross-clamping durations without myocardial perfusion in neonates.

Key Words: congenial heart disease; myocardial protection/cardioplegia; neonate

EVEN THOUGH multidose cardioplegia has been the gold standard for decades, single-dose cardioplegia is being used more commonly and is likely to be an attractive alternative. At North American centers, cold cardioplegia is used in 90% of infants undergoing cardiac surgery, with del Nido cardioplegia being the most popular (38%),[1] whereas 31% of European centers use cold cardioplegia (Custodiol; Dr Franz Köhler Chemie GmbH, Bensheim, Germany).[2] Custodiol is an intracellular cardioplegic solution derived from the solution designed by Bretschneider in the 1970s. It contains histidine (180 mMol/L),

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an excellent buffer in hypothermic conditions; ketoglutarate (1 mMol/L), an intermediate of Kreb's cycle and precursor of nicotinamide dinucleotide phosphate; tryptophan (2 mMol/L) as a membrane stabilizer; and mannitol (30 mMol/L) as an antiedemigen and free radical scavenger. It also contains magnesium chloride (4 mMol/L), sodium chloride (15 mMol/L), and a low calcium concentration (0.015 mMol/L).

Earlier studies have suggested that the implementation of 1 dose of cardioplegia should be well-tolerated in neonates and infants.[3] Both Custodiol and Del Nido cardioplegia are believed to offer myocardial protection for periods of up to 2 to 3 hours.[4-8] In addition, several neonatal procedures, such as arterial switch surgery (ASO), imply aortic division and it is unknown whether repeated ostial cannulation may cause intimal insult and affect long-term results. For all these reasons, together with a better visualization of the coronary arteries and the possibility to perform complex surgeries without interruption, single-dose cold Custodiol cardioplegia has been used for ASO at the authors' unit since 2011. Nevertheless, when comparing the first 30 patients undergoing ASO with single-dose Custodiol with similar cases in whom repeat warm blood was used, the authors' group reported similar outcomes but greater postoperative troponin release.[9] Cardiac troponins are accurate markers of ischemic myocardial damage.[10] If single-dose Custodiol cardioplegia results in greater troponin release, its benefits should be balanced against the risk of ischemic myocardial injury. The present study investigated the association among single-dose Custodiol myocardial no-flow duration and both postoperative troponin release and outcomes in neonates undergoing ASO for simple transposition of the great arteries. The authors also attempted to identify the no-flow cutoff duration for myocardial injury-free single-dose Custodiol administration.

Methods

This retrospective study included all consecutive neonates undergoing ASO for simple transposition of the great arteries between March 1, 2014, and December 31, 2016, at the Necker Sick Children's University Hospital in Paris, France. The Institutional Ethical Committee waived the need for written informed parental consent to perform this retrospective analysis, after de-identification of all patient data.

Anesthesia was induced and maintained using sevoflurane, midazolam, alfentanil, and atracurium. Cardiopulmonary bypass (CPB) was performed with a Stockert-S5 heart-lung machine (Livanova Group, Munich, Germany) and roller pump. The CPB circuit was primed with a mixture comprising 1 U of packed red blood cells, sodium bicarbonate 8.4%, albumin 5%, and 500 IU of unfractionated heparin. All neonates received a bolus of 1 mg/kg dexamethasone after induction of anesthesia. During CPB, the patient's body temperature was lowered to reach moderate hypothermia during aortic cross-clamping. A total of 50 mL/kg of Custodiol was infused at 4°C in the aortic root at cross-clamping and was removed through the right atrium. The decision to deliver additional doses selectively in the coronary ostia was left to the attending surgeon. In addition, 1 surgeon infused additional warm blood cardioplegia before unclamping (hot shot). Conventional ultrafiltration was performed after aortic unclamping in all patients to increase the hematocrit to 40% to 45% and was started earlier in the case of hemodilution because of incomplete removal of cardioplegic solution from the right atrium. A continuous infusion of 0.5 μg/kg/min milrinone was administered to all neonates after aortic unclamping. Epinephrine was started at 0.05 μg/kg/min and then adapted as required. At the end of surgery, the sternum was left open in the case of postoperative low cardiac output syndrome. Patients were believed to have low postoperative cardiac output syndrome in the following situations: (1) in the case of arterial hypotension, increased central venous pressure, left atrial pressure more than 10 mmHg, increased lactic acid concentrations, metabolic acidosis aggravating despite fluid resuscitation and vasoactive-inotropic support, and oliguria; (2) in the case of a rapid hemodynamic deterioration at chest closure unresponsive to inhaled nitric oxide; or (3) in the case of sustained arrhythmia at chest closure unresponsive to external pacing.

Coronary anatomy was considered high risk either in the case of unique coronary ostium (single coronary artery) or in the case of an intramural course and was considered low risk otherwise. The surgical technique used for both ASO and the transfer of intramural coronary arteries was described previously.[11,12] Postoperatively, high-sensitive troponin I was measured using an Abbott ARCHITECT (Abbott, Abbott Park, IL) platform during the following periods: at 20 minutes after unclamping, at admission to the intensive care unit (ICU), every 6 hours within 48 hours, and at the discretion of the attending intensivist afterwards.

Statistical Analysis

The myocardial no-flow duration was defined as the longer of the 2 delays from the end of the Custodiol infusion to either the cross-clamp relief (in case of single-dose cardioplegia) or the beginning of the next cardioplegic infusion (whether cold, warm, crystalloid, or blood). The troponin concentration time integral within 48 hours of surgery (approximated as a sum of products of concentration magnitudes and measurement durations) was taken as a measure of troponin release. An illustration of this methodology is shown in Fig 1, B. The associations among myocardial no-flow duration, troponin release, and all other postoperative variables were explored in univariable and multivariable regression analyses. Because of the major effect of the coronary anatomy on outcome after ASO,[13] and because of the observed significant difference between the myocardial no-flow duration among the 3 attending surgeons, these factors were used for stratification using hierarchical sampling. When independent significant associations were found, the receiver operating curve methodology and the Youden index[14] were used to identify the threshold for the myocardial no-flow duration that could predict an unsuitable outcome. Statistical analysis was performed with the basic package of R software for Windows (www.r-project.org) and the "zoo" (http://zoo.R-Forge.R-project.org) and "lmer" (http://lmer.R-Forge.R-project.org) packages.

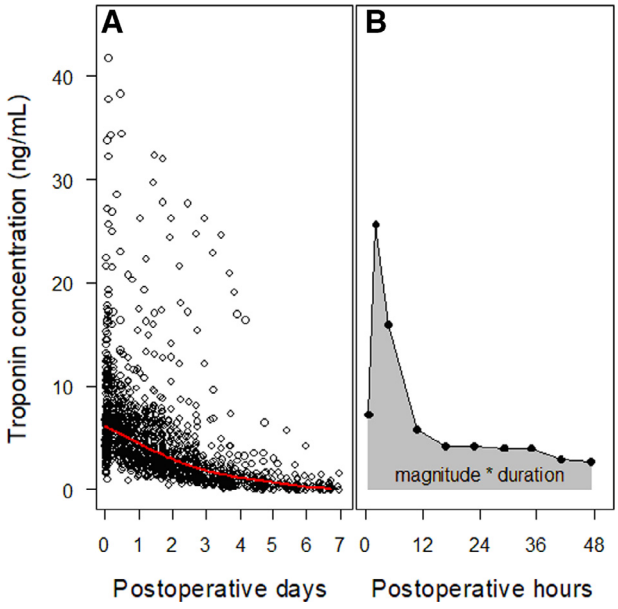

Fig 1. Postoperative high sensitive troponin I concentrations. (A) All troponin concentrations measured during the first postoperative week in the study population. Within 48 hours of surgery, the troponin concentration was measured every 6 hours and at the discretion of the attending intensivist afterwards. The *red line* was drawn by estimating the moving average. (B) Troponin concentrations within 48 hours of surgery in a neonate with low-risk coronary anatomy. The myocardial no-flow duration was 85 minutes, the sternum was closed 7 days after surgery, the duration of mechanical ventilation was 10 days, and the duration of intensive care unit stay was 12 days.

Results

Overall, 103 patients underwent surgery for simple transposition of the great arteries during the study period. Two patients with myocardial infarction after difficulties in coronary transfer were excluded from analysis. The first patient, 4 days old, who had an intramural left coronary artery, was weaned from mechanical ventilation on the first postoperative day and then experienced myocardial infarction a few hours later. The patient required extracorporeal membrane oxygenation (ECMO) for 10 days and died on postoperative day 78 of congestive heart failure and sepsis. The second patient, 7 days old, had signs of myocardial ischemia within minutes of weaning from bypass and underwent a second bypass run for left coronary ostium plasty. The patient required ECMO and died 3 days later of massive stroke. Only 101 patients were analyzed, and their characteristics are shown in Table 1; none of these patients died within 30 days of surgery. One patient was admitted at postoperative day 22 with myocardial infarction because of stenosis of the left coronary ostium and underwent percutaneous angioplasty. The patient required ECMO for 8 days and left the ICU 15 days later.

All patients received single-dose Custodiol cardioplegia, and 24 received an additional hot shot. The scatter plot of all troponin concentrations measured within the first week of surgery is shown in Fig 1, A. Fig 1, B illustrates the calculation of the concentration magnitude × duration product for troponin release within 48 hours in 1 patient. Fig 2 shows the association between the myocardial no-flow duration and the troponin release within 48 hours. The relationship, illustrated by the moving average curve, was approximately linear and was analyzed using linear regression models.

Table 1
Demographic and Outcome Characteristics of the Study Population

Variable	
Age (d)	6.1 ± 5.4
Weight (kg)	3.7 ± 4.6
Low-risk/high-risk coronary anatomy	90 / 11
Cardiopulmonary bypass duration (min)	108.6 ± 54.1
Aortic cross-clamping duration (min)	75.3 ± 34.1
Mean body temperature during aortic cross-clamping (˚C)	31.1 ± 1.7
Received additional warm blood cardioplegia before aortic unclamping	24 (0.24)
Myocardial no-flow duration (min)	60.4 [51.1-62.3]
Delayed sternal closure	32 (0.32)
Delay to sternal closure (d)	3.9 ± 1.6
Highest postoperative troponin concentration within 48 h of surgery (ng/mL)	11.7 ± 8.6
Duration of mechanical ventilation (d)	4 [3-6]
Duration of inotropic support (d)	5 [4-6]
Duration of ICU stay (d)	7 [5-8]

NOTE. Data are presented as mean ± standard deviation, as medians and interquartile ranges, or as numbers and proportions, unless stated otherwise.
Abbreviation: ICU, intensive care unit.

The myocardial no-flow durations were, on average, 50.8 ± 6.7 minutes, 63.1 ± 7.5 minutes, and 85.2 ± 14.2 minutes

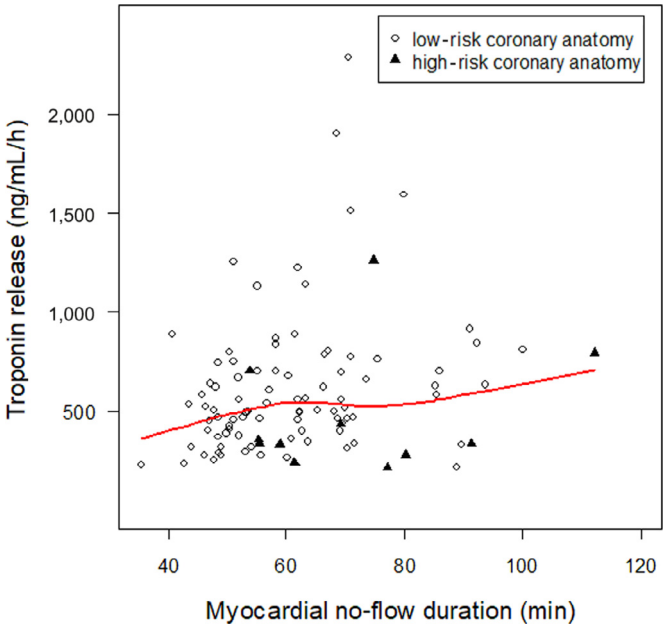

Fig 2. Association between the myocardial no-flow duration and the high sensitive troponin I concentration × duration product (troponin release) within 48 hours of surgery. The *red line* was drawn using a moving average curve. The coronary anatomy was considered high risk when either the left coronary artery emanated from a single right coronary artery or in the case of an intramural course or low risk otherwise. *Triangles* illustrate the cases with high-risk coronary anatomy, and *circles* illustrate the cases with low-risk coronary anatomy.

among the 3 attending surgeons ($p < 0.001$). In univariable analysis, the troponin release was found to be associated with the CPB duration (regression coefficient 15.5 ± 6.6; p = 0.02), cross-clamping duration (regression coefficient 20.3 ± 10.2; p = 0.05), and myocardial no-flow duration (regression coefficient 73.1 ± 32.0; p = 0.02). Troponin release was independent of the patient's age and weight, mean temperature during cross-clamping, and whether or not the sternum was left open. In multivariable analysis, the troponin release was associated with the myocardial no-flow duration (regression coefficient 73.1 ± 34.5; p = 0.04) and was not associated with the durations of CPB and cross-clamping.

The associations among the myocardial no-flow duration, the delay to sternal closure, and weaning from mechanical ventilation are illustrated by the scatter plots in Fig 3. The long duration of mechanical ventilation seen in a 2-day-old patient with low-risk coronary anatomy, who received single-dose Custodiol and a hot shot (which resulted in a myocardial no-flow duration of 38 min and 65 min of aortic cross-clamping) was likely the result of his low weight (2.9 kg) and postoperative pulmonary hypertension. After stratification, the univariable regression showed that the delayed sternal closure was associated with both the patient's age (regression coefficient 0.02 ± 0.007; p = 0.03) and the myocardial no-flow duration (regression coefficient 0.008 ± 0.003; p = 0.03). The duration of mechanical ventilation was associated with the patient's age (regression coefficient 0.15 ± 0.04; p = 0.002) and open chest (regression coefficient 1.3 ± 0.6; p = 0.02) and only weakly with the myocardial no-flow duration (regression coefficient 0.03 ± 0.01; p = 0.08). The duration of inotropic support was associated with age (regression coefficient 0.2 ± 0.03; p = 0.01), myocardial no-flow duration (regression coefficient 0.05 ± 0.01; p = 0.002), and open chest (regression coefficient 2.005 ± 0.5; p = 0.003). The duration of ICU stay was associated with age (regression coefficient 0.2 ± 0.1; p = 0.003) and only weakly with the myocardial no-flow duration (regression coefficient 0.04 ± 0.06; p = 0.07). After stratification according to the coronary anatomy, there was no significant association found among the hot shot administered before unclamping of the aorta, troponin release, and any of the outcomes. The results of the stratified multivariable analysis are shown in Table 2, in which odds ratios were calculated for the upper quartile of the durations of mechanical ventilation, inotropic support, and ICU stay.

Table 3 shows the results of the receiver operating curve analysis for a delayed sternal closure requirement and for long duration of mechanical ventilation (>6 d) (ie, within the upper quartile of all ventilation durations). Overall, 78% of all patients with a myocardial no-flow duration less than 73 to 74 minutes had a good tolerance of sternal closure, and 88% had a duration of mechanical ventilation of <6 days. Among patients with a myocardial no-flow duration exceeding 74 minutes, 82% had a delayed sternal closure.

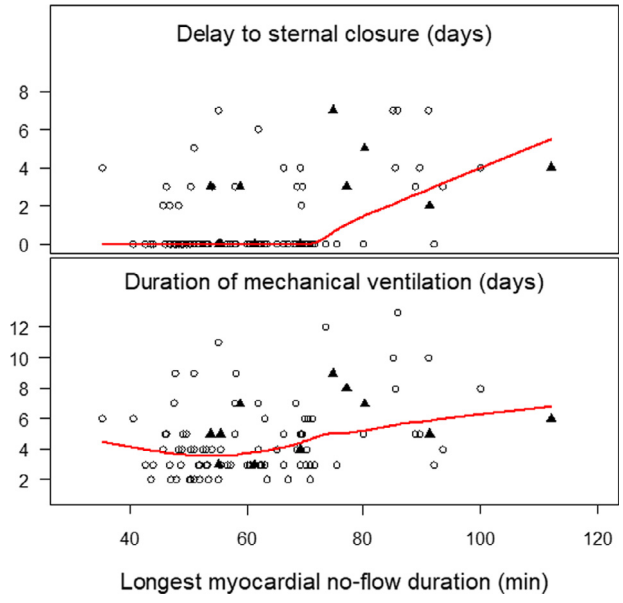

Fig 3. Association between the myocardial no-flow duration and postoperative outcomes. The *red line* was drawn using a moving average curve. *Triangles* illustrate the cases with high-risk coronary anatomy (ie, either the left coronary artery emanated from a single right coronary artery or intramural course). *Circles* illustrate the cases with low-risk coronary anatomy.

Discussion

To date and to the authors' knowledge, this is the first study to focus on the effect of the prolongation of the dosing interval on specific indicators of myocardial ischemia when cold Custodiol cardioplegia was used. The present study demonstrated a proportionate increase in troponin release with the lengthening of the myocardial no-flow duration, independently of the CPB and aortic cross-clamping durations. From the present data it was possible to derive a re-injection interval cutoff of about 73 to 74 minutes, beyond which there was a significantly greater probability for delayed sternal closure requirement and longer mechanical ventilation durations. Such events are a possible reflection of postoperative low cardiac output linked with less adequate myocardial protection. Therefore, the present study's results suggest that the advantages of single-dose Custodiol need to be counterbalanced against the potentially greater risk of myocardial damage during long cross-clamping durations.

Repeat blood-based cardioplegia has become the gold standard in adults undergoing cardiac surgery with aortic cross-clamping.[15] Despite the results of a meta-analysis showing equivalent myocardial protection with intermittent blood and single-dose crystalloid cardioplegia,[16] the use of single-dose Custodiol in adults usually is restricted to minimally invasive or complex cardiac surgeries.[17,18] Blood-based cardioplegia is the most popular cardioplegia in pediatric cardiac surgery, too, as demonstrated by several recent surveys among pediatric cardiac centers.[1,2,19] The 2 most recent surveys[1,2] confirmed the perception that both the del Nido and Custodiol solutions can offer appropriate myocardial protection for long dosing intervals. Among North American pediatric surgeons, however, only 7% use Custodiol, and none uses single-dose Custodiol regardless of the cross-clamping duration.[1] This strategy is progressively becoming popular in Europe,[4,9,20] even for long cross-clamping durations.

Table 2
Results of Multivariable Analysis of the Relationship Between Postoperative Outcome and Intraoperative Parameters

	Delayed Sternal Closure	Duration of Mechanical Ventilation >6 d	Duration of Inotropic Support >7 d	Duration of Intensive Care Unit Stay >8 d
Variable	Odds ratios and 95% confidence intervals			
Age (wk)	1.12 (1.01-1.25)	1.14 (1.03-1.25)	1.17 (1.08-1.28)	1.16 (1.04-1.29)
Myocardial no-flow duration (per 15-min increment)	1.14 (1.009-1.28)	1.10 (1.01-1.20)	1.08 (0.99-1.16)	1.04 (0.96-1.13)
Delayed sternal closure	N/A	1.24 (1.05-1.47)	1.12 (0.96-1.31)	N/A

NOTE. Analyses used logistic regression and were stratified according to the coronary anatomy and the attending surgeon. The cutoff thresholds for the duration of mechanical ventilation, inotropic support, and intensive care unit stay correspond to their upper quartile, respectively. Statistically significant results are shown in italic.

Table 3
Receiver Operating Curve Analysis of the Association Among Myocardial No-Flow Duration, Requirement for a Delayed Sternal Closure, and Mechanical Ventilation Duration Longer Than 6 Days

Outcome Variable	ROC Area	Myocardial No-Flow Threshold Duration*	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Delayed sternal closure	0.675 (0.545-0.804)	74 min	0.44	0.96	0.82	0.78
Mechanical ventilation >6 d	0.674 (0.535-0.814)	73 min	0.47	0.89	0.50	0.88

Abbreviation: ROC, receiver operating curve.
* Identified using the Youden index.

Interestingly, the single-dose strategy seems to be restricted to neonates.[1] Earlier studies showed that the immature myocardium is more tolerant of unprotected normothermic ischemia compared with the mature myocardium.[21] The rationale for a single-dose cardioplegia strategy also is supported by experimental work in neonatal hearts that reported greater postreperfusion myocardial edema with repeat cardioplegia.[22] Two recent studies in neonates showed that, compared with repeat blood-based cardioplegia, the use of single-dose crystalloid cardioplegia resulted in better postoperative cardiac output[23] and in a lower mortality risk after cross-clamping durations >90 minutes.[24]

Results of previous work suggested that there was a critical myocardial no-flow duration in normothermic conditions of 13 minutes, beyond which there was a risk for myocardial ischemia.[25] Based on good clinical tolerance, the dosing interval for warm blood cardioplegia in children was progressively extended to 15 minutes,[26,27] 25 minutes,[28] and even 35 minutes.[29] The good tolerance of cold Custodiol cardioplegia with even longer no-flow durations is most likely owing to a combination of myocardial hypothermia (which further decreases the myocardial oxygen consumption) and the excellent buffer effect of histidine (superior to that of bicarbonate in hypothermic conditions).[30] Nevertheless, long dosing intervals could result in high-energy phosphate depletion, intracellular acidosis,[31] and rewarming of a very small heart because of reduced thermal inertia.[32]

Most of the pediatric publications on single-dose Custodiol cardioplegia base their safety statements on postoperative outcome. Hard clinical outcomes such as mortality, postoperative myocardial infarction, requirement for ventricular assistance, or time to extubation and discharge are multifactorial and lack specificity. In addition, mortality after ASO has decreased to 2.7% during the last decade.[33] Small studies lack statistical power, to identify the risk of myocardial damage as assessed by postoperative mortality. Cardiac troponins are specific markers of myocardial damage[10] and accurate predictors of outcomes after ASO.[34] A previous study[9] by the authors of the present study and a very recent study of single-dose Custodiol in neonatal ASO[20] reported greater troponin concentrations compared with repeat blood cardioplegia. In the previous study, the authors of the present study found a significant linear increase in troponin release parallel with the increase in the no-flow duration. Beyond about 73 to 74 minutes, the probability of occurrence of a low cardiac output, as assessed by the delay to close the chest, was 82%. This cutoff duration was longer than the average 40-minute dosing interval reported by North American surgeons when using cold crystalloid cardioplegia in infants[1] and was shorter than the average durations of 93 and 98 minutes reported in other European pediatric cardiac centers when using Custodiol.[4,20] The 73- to 74-minute cutoff identified in that study provided excellent negative predictive value, suggesting that it is safe to restrict the myocardial no-flow duration to this time range.

In an attempt to adjust for the surgical experience and because of the significant differences observed in the average myocardial no-flow durations among surgeons, the statistical analysis used stratification on the attending surgeons. However, practices differ among surgeons and institutions, and the length of mechanical ventilation and ICU stay is directly related to whether the patient experienced a delayed sternal closure. Unfortunately, the small sample analyzed in the present study did not allow for the performance of an accurate analysis for each subgroup operated on by the same surgeon.

Limitations

The present study is single-center based, and the retrospective design requires that the validity of the findings be considered with caution. Concomitant neonatal comorbidities, not taken into account in the present study, could have biased the interpretation of the association between the myocardial no-flow duration and postoperative outcomes, which are known to be multifactorial. In addition, the experience of the attending surgeon, a decisive factor for the outcome after ASO, could have biased the results despite the statistical adjustment used in the present study.

Conclusion

Despite its widespread use in Europe, the adequacy of myocardial protection offered by a single dose of Custodiol might be a subject of concern in patients with very long cross-clamping durations. The better visualization of the coronary arteries and the possibility to perform complex surgeries without interruption are indisputable benefits; however, these advantages should be balanced against the risk of myocardial ischemia, and it is likely that there is an optimal dosing interval for cold Custodiol cardioplegia. The threshold myocardial no-flow duration derived in the present study needs to be validated in larger, multicenter investigations.

Conflict of Interest

The authors have no conflict of interest to declare.

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