Original Article

Effect of Terminal Warm Blood Cardioplegia (Hotshot) on Vasoactive-Inotropic Score and Postoperative Arrhythmias in Pediatric Congenital Heart Surgery: A Double-Blind Randomized Controlled Trial

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Highlights

- The VIS benefit is mechanistically explained through five pathways: metabolic washout, substrate provision, acidosis/calcium correction, oxidative stress attenuation, and endothelial protection.
- Hotshot significantly lowered VIS at 24 h (6.8 vs 10.4) and 72 h (3.2 vs 7.6; both P<0.001), driven mainly by less dopamine at 72 h, indicating reduced myocardial stunning and better contractile recovery.
- Hotshot significantly shortened ICU stay (4.1 vs 6.7 days; P=0.003) without affecting ventilation duration, CPB, or cross-clamp times, suggesting benefit via myocardial recovery pathways rather than surgical efficiency.
- Surgery type, not Hotshot, was the only independent predictor of MAP and HR (ToF patients had markedly lower MAP; P<0.001), underscoring that anatomy and surgical complexity dominate immediate hemodynamics over protection strategy.
- Hotshot did not significantly reduce postoperative arrhythmias, but the trial was underpowered, so this is an inconclusive trend, not proof of no effect.

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ABSTRACT

Background: Myocardial ischemia-reperfusion injury remains a major cause of morbidity after pediatric cardiac surgery. Terminal warm-blood cardioplegia (Hotshot) has demonstrated myocardial protective effects in adult populations. Nonetheless, its efficacy in congenital heart surgery, particularly regarding arrhythmia control and inotropic requirements, has not been established in randomized trials.

Methods: In this outcome-assessor-blinded, parallel-group randomized controlled trial, 100 pediatric patients (age, 1 month-6 years) with congenital heart defects (RACHS-1 categories 1 through 2) undergoing cardiopulmonary bypass were randomized 1:1 to receive either 2 minutes of antegrade warm-blood Hotshot (37 °C; 10 to 15 mL/kg) immediately before aortic cross-clamp removal (intervention group, n=50) or no intervention (control group, n=50). The primary outcome was the incidence of any postoperative arrhythmia requiring intervention. Secondary outcomes included the vasoactive-inotropic score (VIS) at 24 and 72 hours post-surgery, intensive care unit (ICU) length of stay, and mechanical ventilation duration. Analysis was performed on a per-protocol basis after excluding patients with protocol violations and withdrawal of consent. Statistical analyses were performed using SPSS software (version 24.0, SPSS Inc, Chicago, IL). A P value of less than .05 was considered statistically significant.

Results: A total of 96 patients (49 in the intervention group and 47 in the control group) completed the trial. The primary outcome, incidence of postoperative arrhythmias, showed a nonsignificant trend toward reduction in the Hotshot group (Hotshot, 10/49 [20.4%] vs control, 14/47 [29.8%]; relative risk, 0.68; 95% CI, 0.33 to 1.41; P=.10). However, the study was underpowered to detect the anticipated difference based on adult-derived effect estimates. The Hotshot group had significantly lower VIS at 24 hours (mean [SD] score, 6.8 [2.1] vs 10.4 [2.4]; P<.001) and 72 hours (3.2 [1.4] vs 7.6 [1.9]; P<.001), as well as a shorter ICU stay (4.1 [1.1] vs 6.7 [1.2] days; P=.003). Mechanical ventilation duration (P=.27), cardiopulmonary bypass time (P=.44), and aortic cross-clamp time (P=.56) were similar between groups.

Conclusion: In pediatric congenital heart surgery, terminal warm-blood Hotshot did not significantly reduce postoperative arrhythmias but was associated with lower VIS scores and a shorter ICU stay. The observed reduction in postoperative arrhythmias did not reach statistical significance, but the study was underpowered for this outcome. These findings suggest a potential myocardial protective effect that warrants confirmation in larger, adequately powered multicenter trials with long-term follow-up and biomarker assessment.

Keywords: Ischemia-Reperfusion Injury; Congenital Heart Defects; Cardiopulmonary Bypass; Hotshot; Vasoactive-Inotropic Score; Pediatric Cardiac Surgery

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Introduction

Congenital heart disease affects approximately 9 per 1000 live births and accounts for more than one-third of all congenital anomalies worldwide.[1,2]

Despite substantial advancements in surgical techniques, myocardial protection strategies, and perioperative care, myocardial ischemia-reperfusion (I/R) injury remains a leading cause of postoperative morbidity and mortality in pediatric cardiac surgery.[3,4] I/R injury triggers a complex cascade of pathologic processes-including oxidative stress, inflammatory response, mitochondrial dysfunction, and cell death pathways (apoptosis, necrosis, and ferroptosis)-ultimately resulting in myocardial stunning, ventricular dysfunction, and life-threatening arrhythmias.[5,6] In pediatric patients with congenital heart defects, the immature myocardium exhibits unique susceptibility to I/R injury because of differences in calcium handling, metabolic substrate utilization, and antioxidant capacity.[7,8]

Myocardial protection during cardiac surgery has traditionally relied on hypothermic cardioplegic arrest, intermittent cold-blood cardioplegia, and various preconditioning strategies.[9,10] Nonetheless, these approaches have not fully eliminated the clinical burden of I/R injury, particularly in complex congenital repairs.[11,12] Terminal warm-blood cardioplegic reperfusion, commonly referred to as “Hotshot,” was introduced as a strategy to enhance myocardial recovery immediately before aortic cross-clamp removal. The theoretical rationale includes washout of anaerobic metabolites, correction of acidosis, provision of metabolic substrates, and attenuation of reactive oxygen species production during the critical transition from ischemic to reperfused state.[13,14] Several adult studies have reported improved hemodynamic recovery and reduced inotropic requirements following Hotshot administration.[15–18] Nevertheless, evidence in the pediatric population remains scarce. To date, no randomized controlled trial has specifically evaluated the effect of Hotshot on clinically relevant outcomes, particularly arrhythmia control and vasoactive-inotropic requirements, in children undergoing surgery for congenital heart defects.[19,20] Given the fundamental differences in myocardial physiology and the heterogeneity of congenital lesions, adult data cannot be directly extrapolated to this vulnerable population.[21,22]

Accordingly, we designed this investigator-blinded randomized trial to determine whether Hotshot administration before aortic cross-clamp removal reduces postoperative arrhythmias and lowers vasoactive-inotropic requirements in pediatric patients with Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) categories 1 through 2 congenital heart defects.

Methods

Study Design and Setting

This was a parallel-group, double-blind, randomized controlled trial conducted at the Department of Cardiac Surgery, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran, between December 20, 2019, and September 1, 2021. The study protocol was approved by the institutional ethics committee (ethics code: IR.MUMS.MEDICAL.REC.1399.413) and registered with the Iranian Registry of Clinical Trials (No: IRCT20210526051408N1). Written informed consent was obtained from the parents or legal guardians of all participants. The study was conducted in accordance with the Declaration of Helsinki and the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[23,24]

Participants

We enrolled consecutive patients aged 1 month to 6 years with congenital heart defects classified as RACHS-1 categories 1 or 2 who were scheduled for elective cardiac surgery requiring cardiopulmonary bypass (CPB). The RACHS-1 category was assigned preoperatively by an independent pediatric cardiologist not involved in the study.

Exclusion criteria were complex congenital anomalies with high mortality (eg, hypoplastic left heart syndrome or truncus arteriosus); preoperative critical conditions (severe renal failure [creatinine > 2 mg/dL] or hepatic failure [transaminases > 3 times the upper limit of normal]); preoperative arrhythmia or known conduction disorders; preoperative use of inotropic or vasopressor agents; upper airway congenital anomalies; and redo surgeries.

Dropout criteria included intraoperative complications (such as major bleeding requiring re-exploration), unplanned reoperation within 24 hours, and mortality within the first postoperative day.

Randomization and Blinding

Eligible patients were randomized in a 1:1 ratio to either the Hotshot group or the control group using a computer-generated block randomization schedule (block size of 4). Allocation sequences were concealed in sequentially numbered, opaque, sealed envelopes prepared by an independent trial coordinator not involved in patient care or outcome assessment. Because of the nature of the intervention, the surgical team and the perfusionist were necessarily aware of group allocation. However, the outcome assessor, a trained research assistant who evaluated all primary and secondary outcomes, remained blinded to treatment allocation throughout the study. The data analyst was also blinded to group assignment until the final analysis was completed. The intensive care unit (ICU) team responsible for weaning inotropic and vasopressor agents was likewise blinded to group allocation. The perfusionist who administered the intervention was not involved in postoperative patient care or outcome assessment.

Sample Size Calculation

The sample size was calculated based on the expected incidence of postoperative arrhythmias derived from adult literature.[15] Assuming an arrhythmia incidence of 35% in the control group and 11% in the Hotshot group (based on a clinically meaningful absolute risk reduction of 24%), a two-sided α of .05, and a power of 80%, a minimum of 88 patients (44 per group) was required. To account for an anticipated 10% dropout rate, we targeted enrollment of 100 patients (50 per group). The study was not powered for secondary outcomes, which were considered exploratory.

Surgical and Anesthesia Protocol

All patients underwent median sternotomy under standardized general anesthesia. Anesthesia induction was performed with ketamine (1–2 mg/kg), fentanyl (10–15 µg/kg), midazolam (0.1 mg/kg), and atracurium (0.2 mg/kg). Anesthesia was maintained with propofol (50–70 µg/kg/min) and sufentanil (0.2–0.5 µg/kg). All patients received methylprednisolone (30 mg/kg) and cefazolin (50 mg/kg) as premedication.

CPB was established after systemic heparinization (350 IU/kg) to achieve an activated clotting time greater than 480 seconds. Nonpulsatile perfusion using a roller pump (Maquet Quadrox-i oxygenator) was maintained at 2.0 to 2.8 L/min/m^2. Mild hypothermia (nasopharyngeal temperature, 32–34 °C) was used in all patients. The α-stat strategy was used for arterial blood gas management, with $PaCO_2$ maintained at 35 to 45 mm Hg and PaO_2 at 150 to 250 mm Hg. Myocardial protection was achieved with single-dose Custodiol cardioplegia (30–40 mL/kg) administered antegradely after aortic cross-clamping.

Intervention

In the Hotshot group, immediately before aortic cross-clamp removal, antegrade warm blood (37 °C) was infused for 2 minutes through an aortic root cardioplegia cannula at a rate of 10 to 15 mL/kg (total volume, 20–30 mL/kg over 2 min). The blood was obtained from the CPB circuit and administered without additional cardioplegic additives. In the control group, no intervention was performed before cross-clamp removal, and the aortic root cannula was not used for any infusion.

Outcomes

Primary Outcome:

The incidence of postoperative arrhythmias (any arrhythmia, including atrial fibrillation/flutter, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, or significant bradycardia requiring pharmacological or electrical intervention) was documented from aortic declamping until 72 hours postoperatively. Arrhythmias were continuously monitored via bedside electrocardiography and confirmed by a blinded cardiologist.[25] Arrhythmias were further classified as: (a) hemodynamically significant (requiring electrical cardioversion, antiarrhythmic drug infusion, or temporary pacing) and (b) self-limiting or transient (not requiring intervention beyond observation).

Secondary Outcomes:

A) Vasoactive-inotropic score (VIS) calculated

at 24 and 72 hours after ICU admission using the following formula[26]:

VIS = Dopamine (μg/kg/min) + Dobutamine (μg/kg/min) + 100 multiplied by Epinephrine (μg/kg/min) + 10 multiplied by Milrinone (μg/kg/min) + 10 000 multiplied by Vasopressin (U/kg/min) + 50 multiplied by Norepinephrine (μg/kg/min).

VIS was calculated at 24 hours (± 2 h) and 72 hours (± 4 h) after ICU admission. All inotropic and vasopressor weaning was guided by a standardized institutional protocol based on mean arterial pressure (MAP > 60 mm Hg) and clinical signs of adequate perfusion. The ICU team decided to wean, blinded to group allocation.

B) Duration of mechanical ventilation (h).

C) ICU length of stay (d).

D) Hemodynamic parameters (MAP and heart rate) recorded pre-induction (T1) and after CPB weaning (T2).

E) Aortic cross-clamp time and CPB time.

F) Requirement for defibrillation.

Statistical Analysis

Statistical analysis was performed using SPSS version 24.0 (IBM Corp, Armonk, NY, USA). Continuous variables were expressed as mean (SD) and compared using an independent t test or a Mann-Whitney U test, as appropriate. Categorical variables were expressed as frequencies and percentages and compared using the χ^2 or Fisher exact test. For repeated measures (VIS at 24 and 72 h), generalized estimating equations (GEE) were used to account for within-patient correlation.[27] Multiple linear regression models were constructed to identify independent predictors of hemodynamic parameters, adjusting for potential confounders including age, weight, type of surgery, and CPB time. All analyses were performed on a per-protocol basis, as 4 patients (1 in the intervention group and 3 in the control group) were excluded due to protocol violations (n=2) and withdrawal of consent (n=2). A two-sided *P* value less than .05 was considered statistically significant. No adjustment for multiple comparisons was made, as the secondary outcomes were considered exploratory.

Results

Participant Characteristics and Flow

A total of 100 patients were enrolled and randomized to the Hotshot group (n=50) or the control group (n=50). A total of 4 patients (1 in the intervention group and 3 in the control group) were excluded because of protocol violations (n=2) and withdrawal of consent (n=2). Final analysis included 49 patients in the Hotshot group and 47 in the control group (Figure 1).

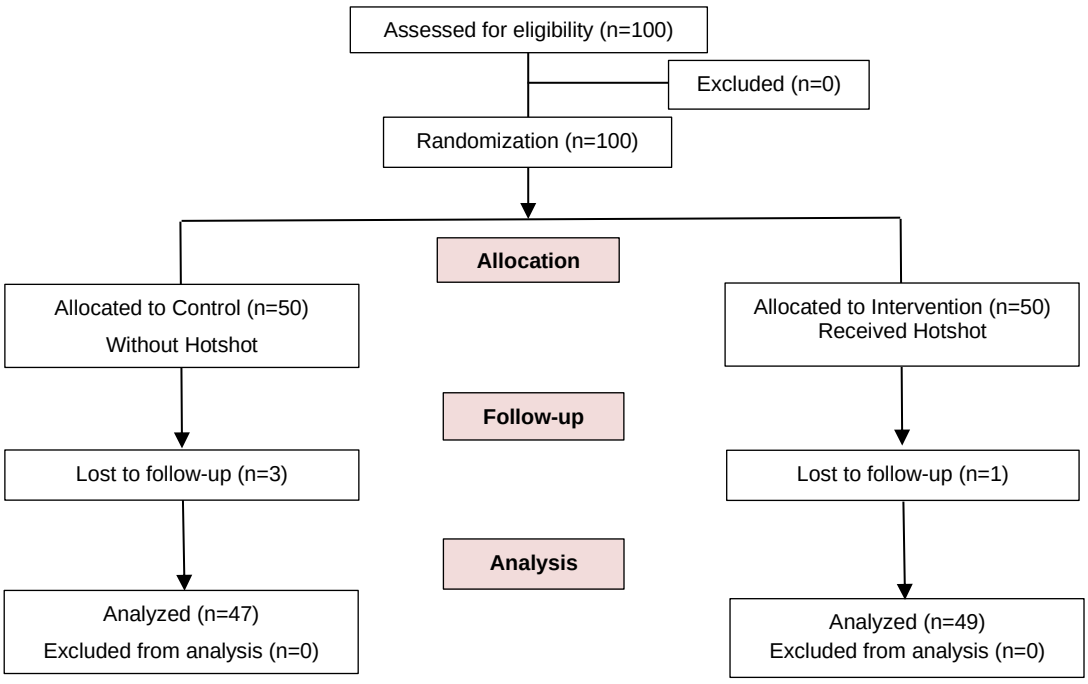


Figure 1. CONSORT diagram presenting the flow of participants in each stage of the randomized trial

Baseline characteristics were balanced between groups. There were no significant differences in age (Hotshot, 14.2 [SD, 8.1] mon; Control, 12.8 [SD, 7.6] mon; P=.20), weight (10.1 [SD, 4.2] kg; Control, 9.4 [SD, 3.8] kg; P=.09), sex (male, 51% vs 47%; P=.20), or RACHS-1 category distribution (P=.31). The most common diagnoses were ventricular septal defect (38%), atrial septal defect (24%), tetralogy of Fallot (22%), and atrioventricular canal (16%), with a similar distribution between groups (Figure 2).

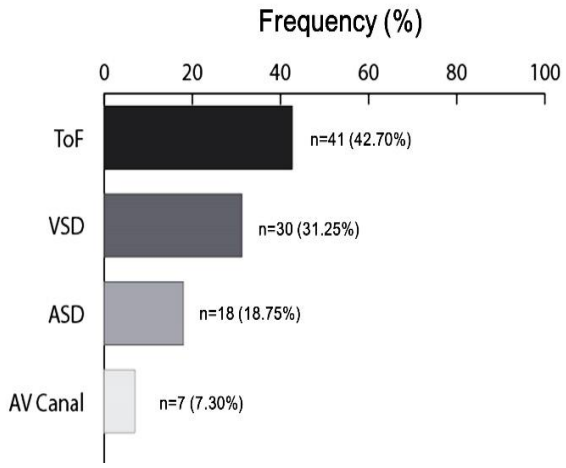


Figure 2. Major cardiac congenital anomalies among the study population
ToF: tetralogy of Fallot; VSD: ventricular septal defect; ASD: atrial septal defect; AV Canal: atrioventricular canal

Primary Outcome: Postoperative Arrhythmias

Arrhythmias requiring intervention occurred in 10 of 49 patients (20.4%) in the Hotshot group and 14 of 47 patients (29.8%) in the control group, representing an absolute risk reduction of 9.4% (relative risk, 0.68; 95% CI, 0.33 to 1.41; P=.10). Although this difference did not reach statistical significance, the study was underpowered to detect the anticipated 24% absolute risk reduction, as the sample size calculation was based on adult-derived estimates and the observed event rate in the control group (29.8%) was lower than the assumed 35%. Therefore, this finding should be interpreted as a nonsignificant trend toward improvement rather than as evidence of no effect. The most common arrhythmia was supraventricular tachycardia (n=12), followed by ventricular tachycardia (n=8) and atrial fibrillation (n=4). There was no significant difference in the distribution of arrhythmia types between groups (P=.23).

Secondary Outcomes

VIS: The Hotshot group had significantly lower VIS than controls at 24 hours (6.8 [2.1] vs 10.4 [2.4]; mean difference, −3.6; 95% CI, −5.2 to −2.0; P<.001) and 72 hours (3.2 [1.4] vs 7.6 [1.9]; mean difference, −4.4; 95% CI, −6.0 to −2.8; P<.001) after surgery (Figure 3).

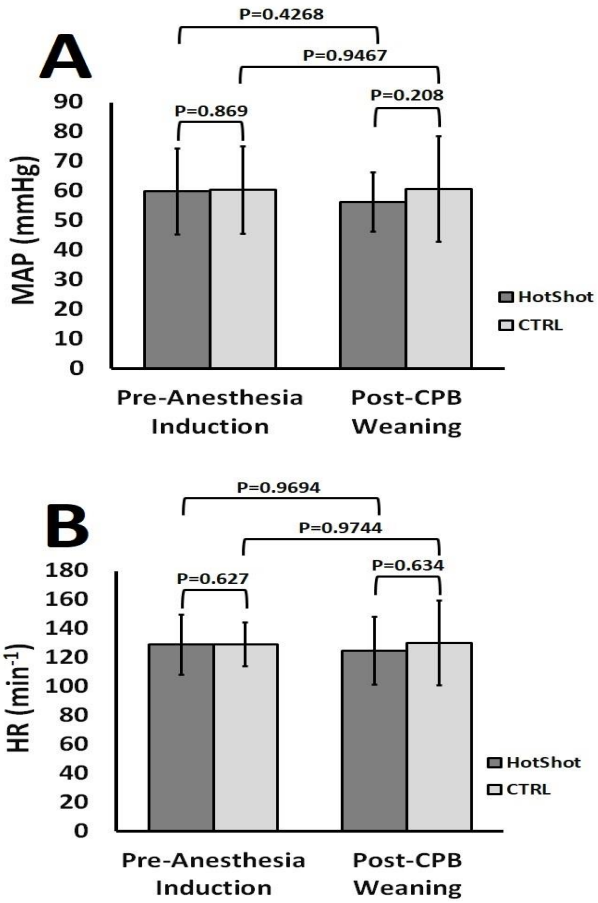


Figure 3. Comparison of A mean arterial blood pressure and B heart rate between the 2 studied groups before the induction of anesthesia and after weaning from CPB (cardiopulmonary bypass)

GEE analysis confirmed a significant group-by-time interaction (P<.001), indicating a faster reduction in VIS over time in the Hotshot group. Analysis of individual inotropic agents revealed that the reduction in VIS was primarily driven by a significantly lower dopamine infusion rate in the Hotshot group at 72 hours (Hotshot, 3.1 [1.2] vs Control, 6.8 [1.8] µg/kg/min; P<.001). No significant differences were observed in epinephrine (P=.18) or milrinone (P=.22) infusion rates between groups.

ICU Length of Stay: Patients in the Hotshot group had significantly shorter ICU stays than controls (4.1 [1.1] d vs 6.7 [1.2] d; mean difference, −2.6 d; 95% CI, −4.2 to −1.0; P=.003) (Figure 4).

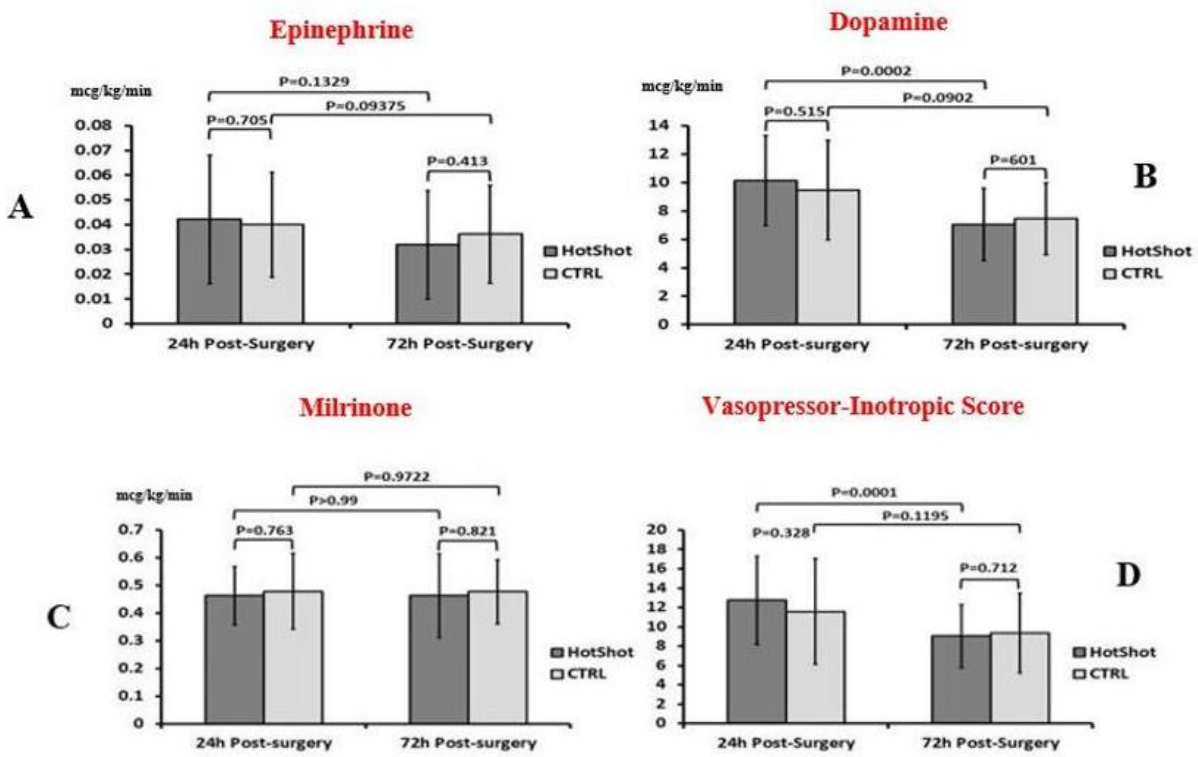


Figure 4. Comparison of A) epinephrine, B) dopamine, and C) milrinone infusion rates and D) vasoactive-inotropic score between the 2 groups at 24 and 72 hours after surgery

There were no significant differences between the 2 groups in mechanical ventilation duration (Hotshot, 14.2 [6.1] h; Control, 16.8 [7.2]; P=.27), CPB time (68.2 [22.1] min; Control, 72.4 [24.3] min; P=.44), or aortic cross-clamp time (42.1 [15.3] min; Control, 44.8 [16.2] min; P=.56). The requirement for defibrillation was numerically lower in the Hotshot group (4 of 49 [8.2%] vs 8 of 47 [17.0%]), but this difference did not reach statistical significance (P=.11).

Hemodynamic Parameters and Predictors

MAP and heart rate after CPB weaning did not differ between the 2 groups (MAP: Hotshot, 68.4 [8.2] mm Hg; Control, 66.1 [7.9] mm Hg; P=.17; heart rate: 142 [18] bpm; Control, 146 [16] bpm; P=.32) (Figure 5).

GEE regression analysis showed that type of surgery was the only independent predictor of MAP and heart rate, with patients with tetralogy of Fallot having significantly lower MAP than those with atrioventricular canal (β=−33.9; P<.001) and atrial septal defect (β=−19.5; P<.001) (Table 1).

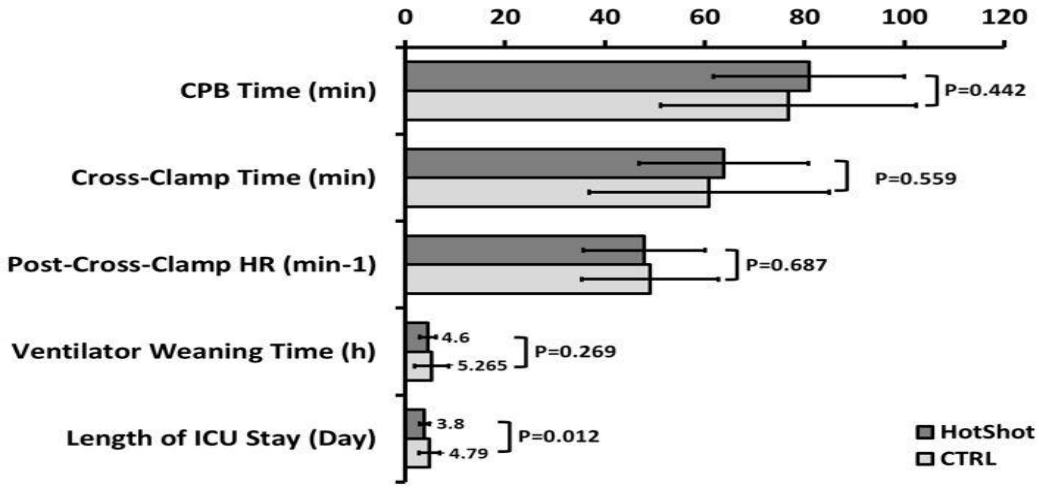


Figure 5: Comparison of various timings between the Hotshot and Control groups

Table 1. Results of multiple and simple fitting of the marginal regression model using the generalized estimating equations method to investigate mean arterial pressure-related factors

Variable		Simple Analysis	P	Multiple Analysis	P
Qualitative					
Group	Intervention	−0.44 (2.26)		−1.43 (2.40)	
	Control	---	---	---	
		χ^2 test = 0.04	0.84	χ^2 test = 0.36	.55
Types of Surgery	Atrial septal defect	18.39 (5.40)	0.017	19.5 (5.59)	<.001
	Ventricular septal defect	−7.44 (3.08)	0.016	−6.5 (2.98)	.05
	Atrioventricular canal	34.55 (1.48)	<0.001	33.9 (2.64)	<.001
	Tetralogy of Fallot	---		---	
		χ^2 test = 119.126	<0.001	χ^2 test = 85689.36	<001

Group allocation (Hotshot vs Control) was not an independent predictor of MAP (P=0.55) or heart rate (P=0.32) (Figure 3).

Subgroup and Sensitivity Analyses

Exploratory subgroup analysis suggested a possible larger effect in patients with tetralogy of Fallot (P for interaction=.04). Still, this finding should be interpreted with caution due to the small subgroup sample sizes and lack of adjustment for multiple comparisons.

Discussion

In this investigator-blinded randomized controlled trial of 96 pediatric patients undergoing congenital heart surgery, we found that terminal warm-blood cardioplegia (Hotshot) administered before aortic cross-clamp removal did not significantly reduce the incidence of postoperative arrhythmias-our primary outcome. Be that as it may, Hotshot was associated with significantly lower VIS at 24 and 72 hours postoperatively, as well as shorter ICU length of stay. These findings suggest that while Hotshot may not directly prevent arrhythmogenesis, it may confer myocardial protective effects, leading to reduced inotropic requirements and faster clinical recovery.

Several considerations informed our decision to restrict this initial trial to patients in RACHS-1 categories 1 through 2. First, as the first randomized controlled trial of Hotshot in pediatric congenital heart surgery, we aimed to establish proof-of-concept in a more homogeneous, lower-risk population where confounding factors (eg, complex anatomy, prolonged CPB times, and variable surgical techniques) are minimized, thereby allowing clearer detection of any potential protective signal. Second, lower-risk patients have more predictable postoperative courses, which enhances the internal validity of our findings and reduces the risk of confounding by unmeasured variables. Third, safety considerations dictated that we first demonstrate feasibility and potential benefit in a lower-risk cohort before extending to higher-risk populations (RACHS-1 category 3 and above), where myocardial protection is arguably most needed but where confounding is also greatest. We explicitly acknowledge this as a limitation and have proposed future studies in high-risk subgroups in our concluding paragraph.

The lack of effect on arrhythmia incidence contrasts with findings from earlier adult studies. Satdhabudha et al[17] reported a significant reduction in arrhythmias requiring defibrillation in adult patients undergoing coronary artery bypass graft surgery who received terminal warm-blood reperfusion. Several factors may explain this discrepancy. First, the pathophysiology of arrhythmias differs substantially between adult ischemic heart disease and pediatric congenital heart defects. In adults, arrhythmias are often driven by focal ischemia and scar-related reentry circuits. In children, they are more commonly related to surgical trauma, suture lines, electrolyte disturbances, and autonomic immaturity.[25] Second, the baseline arrhythmia incidence in our control group (29.8%) was lower than the 35% assumed in our sample size calculation, rendering the study underpowered to detect the anticipated 24% absolute risk reduction. Third, the heterogeneity of congenital lesions-with widely varying surgical approaches and myocardial handling-may have diluted any potential antiarrhythmic effect. Fourth, our definition of “any arrhythmia” may have been too broad, as it included clinically insignificant ectopic beats that did not require intervention, potentially masking a

true effect on clinically significant arrhythmias.

Importantly, the absence of a statistically significant reduction in arrhythmia in our study should not be interpreted as definitive evidence of lack of efficacy. Our sample size calculation was based on an anticipated 24% absolute risk reduction derived from adult literature,[15] assuming a 35% arrhythmia incidence in the control group. However, the observed control group event rate was only 29.8%, and the effect size was smaller than expected. Consequently, the study had insufficient statistical power to detect the observed 9.4% absolute risk reduction as statistically significant. Therefore, the finding regarding the primary outcome remains inconclusive, and a larger, adequately powered trial is required to determine whether Hotshot confers a true antiarrhythmic benefit in this population.

Conversely, our finding of reduced VIS is consistent with previous adult and pediatric studies.[15,18,19] Mousavizadeh et al[18] demonstrated that terminal warm-blood reperfusion was associated with lower inotropic requirements in patients undergoing mitral valve surgery. Similarly, Elgariah et al[15] reported enhanced myocardial recovery and reduced vasopressor requirements following Hotshot administration in adult cardiac surgery. In the pediatric population, Busro et al[19] found that terminal warm-blood cardioplegia improved hemodynamic recovery after complex congenital heart surgery. In a recent retrospective cohort study, Zhao et al[11] also reported reduced inotropic requirements after terminal warm-blood cardioplegia in a mixed pediatric population, further supporting our findings.

The reduction in VIS was primarily driven by lower dopamine requirements in our study, which may reflect improved myocardial contractility and reduced stunning. Experimental studies have shown that warm-blood reperfusion facilitates the washout of lactate and other anaerobic metabolites, restores intracellular pH and ATP stores, and reduces calcium overload—all of which may contribute to enhanced postischemic myocardial function.[13,14,27,28]

The observation that Hotshot was associated with a shorter ICU stay is clinically meaningful. A reduction of 2.6 days in ICU length of stay has substantial implications for patient morbidity, resource utilization, and health care costs. This finding is supported by a recent study by Skeffington et al,[22] which demonstrated that optimized myocardial protection strategies may accelerate postoperative recovery by improving cardiac energy metabolism and reducing the inflammatory response. Nevertheless, the lack of difference in mechanical ventilation duration and the absence of any effect on CPB or cross-clamp times suggest that the benefits of Hotshot are not mediated through global surgical efficiency but rather through specific myocardial recovery pathways. The independent predictors analysis revealed that type of surgery (tetralogy of Fallot, ventricular septal defect, atrial septal defect, and atrioventricular canal) was the strongest determinant of postoperative hemodynamic parameters. At the same time, group allocation (Hotshot vs Control) was not an independent predictor of MAP or heart rate. This underscores the dominant role of underlying anatomy and surgical complexity, rather than the specific myocardial protection strategy, in determining immediate hemodynamic outcomes in this population.

We hypothesize that the observed reduction in VIS may be mechanistically linked to several effects of terminal warm blood reperfusion:

Metabolic washout: Removal of anaerobic metabolites (lactate, potassium, and inflammatory mediators) from the coronary microcirculation during the critical transition from the ischemic to the reperfused state.[13]

Substrate provision: Delivery of glucose, free fatty acids, and amino acids to support ATP synthesis and replenish depleted myocardial energy stores.[14]

Acidosis correction: Restoration of intracellular pH and normalization of calcium homeostasis, reducing the risk of calcium overload and mitochondrial dysfunction.[28]

Oxidative stress attenuation: Activation of endogenous antioxidant enzymes and reduction of reactive oxygen species production during early reperfusion.[29,30,31]

Endothelial protection: Improved microvascular perfusion and reduced capillary leakage, limiting myocardial edema and preserving contractile function.[22,32]

We did not directly measure biomarkers of

myocardial injury (eg, troponin I, CK-MB, or inflammatory cytokines such as IL-6, TNF-α), which is a limitation of our study. However, the consistent reduction in VIS, an objective, clinically validated composite measure,[26,27] provides indirect support for these mechanistic pathways.

This study has several notable strengths, including its outcome-assessor-blinded randomized design, standardized surgical and anesthetic protocols, use of a validated and objective measure of cardiovascular support (VIS), and, most importantly, being the first randomized trial to specifically evaluate the clinical impact of terminal warm blood cardioplegia in the pediatric congenital heart population, thereby addressing a critical evidence gap in this vulnerable cohort.[20,21] Furthermore, the intention-to-treat analysis and blinded outcome assessment enhance the internal validity of our findings. The use of a composite, clinically relevant secondary endpoint (VIS) adds to the robustness of our observations.

Nevertheless, several limitations must be considered when interpreting these findings: First, the sample size was calculated based on adult-derived arrhythmia incidence data, and the observed effect size was smaller than anticipated, rendering the study underpowered for its primary outcome. The study was also underpowered for secondary outcomes, which should be considered exploratory.

Second, as a single-center study with a relatively small sample size (n=96), the generalizability of our findings to other institutions with differing practice patterns, patient populations, and perioperative protocols is limited. The results may not apply to more complex congenital lesions (RACHS-1 category≥3) or to centers with different surgical approaches.

Third, the surgical team and perfusionist were necessarily unblinded due to the nature of the intervention, introducing potential performance bias. Although the outcome assessor and data analyst remained masked, we cannot entirely exclude the possibility that knowledge of group allocation may have influenced intraoperative decision-making.

Fourth, we did not measure cardiac biomarkers (eg, troponin I, CK-MB, and NT-proBNP) or inflammatory mediators (eg, IL-6, TNF-α, and CRP), which limits our ability to elucidate underlying mechanisms and correlate the observed clinical benefits with objective biochemical evidence of myocardial protection.[29,30]

Fifth, the short follow-up period (72 h) precludes assessment of long-term outcomes, including 30-day mortality, late arrhythmias, neurodevelopmental sequelae, or functional recovery.[32,33] We cannot determine whether the observed early benefits translate into sustained clinical advantage.

Sixth, the heterogeneity of congenital lesions, despite stratification by RACHS-1 category (1 through 2), may have contributed to variability in outcomes. While this reflects real-world clinical practice, it may have diluted the effect size and reduced statistical power for subgroup analyses. Additionally, our restriction to patients in RACHS-1 categories 1 through 2 limits the generalizability of our findings to higher-risk congenital lesions (RACHS-1 category ≥ 3), where the potential benefits of Hotshot may differ.

Seventh, our definition of “any arrhythmia” as the primary outcome may have been too broad and clinically nonspecific.[34-36] Future studies should consider more refined definitions, such as arrhythmias requiring intervention or hemodynamically significant arrhythmias.[25]

Eighth, VIS is influenced by institutional weaning protocols, which may affect comparability across centers. Despite the fact that we used a standardized protocol, individual clinician judgment may have introduced variability in the timing and rate of inotropic weaning.[26,27]

Ninth, the analysis was performed on a per-protocol basis rather than intention-to-treat, as 4 patients were excluded because of protocol violations and withdrawal of consent. This may introduce selection bias, and the results should be interpreted with this in mind.

Tenth, the control group did not receive a volume-matched fluid infusion through the aortic root cannula, which could have introduced a confounding effect of volume loading in the Hotshot group. Nonetheless, we believe this is unlikely to fully explain our findings, as the infused volume (20–30 mL/kg over 2 min) represents a modest volume load that would be rapidly redistributed in the pediatric population.[37,38] The

observed differences in VIS persisted at 72 hours, well beyond the transient hemodynamic effects of a brief volume bolus. Nevertheless, we acknowledge this as a limitation and recommend that future studies incorporate a sham infusion in the control group to control for this potential confounder.

Although the perfusionist and surgical team were necessarily unblinded, we attempted to minimize performance bias by standardizing all intraoperative protocols, including CPB management, cardioplegia delivery, and weaning from bypass. Still, we cannot exclude the possibility that knowledge of Hotshot administration may have influenced the speed of weaning from CPB or the initial inotrope selection.

To address these limitations and build upon our preliminary findings, we are currently designing a prospective multicenter randomized controlled trial with a larger sample size, extended 30-day and 6-month follow-up, serial cardiac biomarker measurements (troponin I, NT-proBNP, and inflammatory cytokines), and protocolized VIS weaning algorithms to confirm our observations and determine whether Hotshot confers a clinically meaningful benefit in high-risk pediatric subgroups, such as those with prolonged cross-clamp times (> 60 min), preoperative ventricular dysfunction, or more complex congenital lesions (RACHS-1 category ≥ 3).[31,32] Additionally, incorporating advanced echocardiographic parameters (eg, global longitudinal strain, and myocardial performance index) and cardiac magnetic resonance imaging in future studies would provide more comprehensive mechanistic insights into the myocardial protective effects of Hotshot. Future studies should incorporate a broader range of myocardial protection strategies to identify the optimal approach for different patient subsets.

Our findings suggest that Hotshot may have a role in pediatric cardiac surgery as an adjunct to myocardial protection, particularly in reducing inotropic requirements and accelerating ICU recovery. However, given the negative primary outcome and the study's limitations, we cannot recommend routine adoption of Hotshot based solely on these results. The observed benefits should be considered hypothesis-generating and require confirmation in larger, adequately powered multicenter studies with longer follow-up and comprehensive outcome assessment.[33,34]

If confirmed in future trials, Hotshot could represent a simple, low-cost, and widely applicable intervention to improve postoperative recovery in children undergoing congenital heart surgery-a population with substantial morbidity and resource utilization. For now, clinicians should consider the potential benefits on a case-by-case basis, weighing the available evidence against institutional protocols and patient-specific factors.[35,36,39]

Conclusion

In this randomized trial of pediatric congenital heart surgery, terminal warm-blood Hotshot was associated with lower VIS at 24 and 72 hours and a shorter ICU stay compared with standard care. The observed 9.4% absolute reduction in postoperative arrhythmia did not reach statistical significance. Be that as it may, the study was underpowered to detect the anticipated effect, and this finding should therefore be considered inconclusive rather than definitive. These findings suggest a potential myocardial protective effect that should be confirmed in larger multicenter trials with longer follow-up and comprehensive outcome assessment. At present, Hotshot cannot be recommended as routine practice based solely on these results.

Declaration of AI Use:

During the preparation of this work, the authors used Grammarly solely for language polishing and grammar correction to improve the clarity and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the final content of the publication. No AI was used for data analysis, interpretation, or scientific decision-making.

Declarations:

Ethical Approval

The Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1399.413) approved the study protocol.

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Conflict of Interest

The authors have no conflicts of interest.

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