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Myocardial protection in pediatric cardiac surgery: deep look to the most often used cardioplegic solutions

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Abstract

Background.Cardioplegic arrest is a crucial strategy for myocardial protection in pediatric cardiac surgery. The selection of an optimal cardioplegic solution remains a topic of debate, given the unique physiology of pediatric heart muscle and the diverse range of available solutions. This comprehensive review aims to evaluate and synthesize existing evidence on the effectiveness of different cardioplegic solutions in pediatric myocardial protection.

Methods. A comprehensive literature search was conducted to identify randomized control trials, prospective observational studies, and retrospective analyses focusing on myocardial protection methods in pediatric open-heart surgery. The review encompasses studies involving the four main types of cardioplegia: blood cardioplegia (BCP), St. Thomas (STH) cardioplegia, del Nido (DNC) cardioplegia, and Histidine-tryptophan-ketoglutarate (HTK) cardioplegia.

Results. The literature review includes 3,465 pediatric patients from various studies, with a focus on myocardial injury markers, metabolic outcomes, intraoperative variables, and postoperative outcomes associated with different cardioplegic solutions. Results indicate that DNC may offer benefits in terms of myocardial injury and intraoperative variables, but there is a lack of significant differences in mortality among the four commonly used cardioplegic solutions.

Conclusion. While current evidence does not demonstrate significant mortality benefits among the four cardioplegic solutions in pediatric cardiac surgery, DNC shows promise in mitigating myocardial injury and influencing intraoperative variables. However, the need for well-designed multicenter randomized controlled trials remains to establish clear evidence for myocardial protection in pediatric cardiac surgery.

Keywords: pediatric cardiac surgery; cardioplegia, blood cardioplegia, crystalloid cardioplegia, del Nido cardioplegia, Histidine-tryptophan-ketoglutarate cardioplegia, St. Thomas cardioplegia.

1. Introduction

Cardioplegic arrest is a commonly employed strategy for myocardial protection [1]. Initially, cardioplegia for infant and pediatric patients followed the same principles as that used for adults, with adjustments made for volume, flow, and pressure [1, 2]. Presently, cardioplegic solutions used in pediatric clinical practice are categorized based on various parameters such as temperature (cold, tepid or warm), composition (crystalloid or blood), delivery method (anterograde, retrograde or combined), and substances contained within the solution (e.g., glucose with insulin) [3, 4]. These cardioplegic solutions can also be divided into two primary groups: those based on extracellular components with high levels of potassium, magnesium and bicarbonate, and those based on intracellular electrolytes [5]. Despite the wide range of available cardioplegic solutions, there is an ongoing debate regarding the most effective option for pediatric myocardial protection.

The physiology of pediatric heart muscle differs significantly from that of the adult myocardium. There have been contrasting descriptions of the immature heart, with some studies suggesting it is more tolerant to ischemia [6-8], while others indicate it is less tolerant [9, 10]. This disparity may be attributed to the potential impact of the cardioplegia solution on the efficacy of myocardial protection, rather than solely relying on the physiology of the neonatal heart [11]. Another crucial factor is the increased calcium sensitivity is increased, and reduced ability to scavenge free radicals in the immature heart, which heightens the risk of ischemic injury [6-8]. Furthermore, the immature hearts demonstrates a preference for utilizing glucose as a substrate and accumulates glycogen, potentially increasing its resistance to ischemic damage [6-8].

Myocardial protection becomes particularly challenging in certain cases, such as lengthy and complex procedures or pediatric patients with preoperative damaged myocardium [12]. In such situations, the selection of an optimal cardioplegic solution poses more questions than answers. Experimental studies have demonstrated a preference for single-dose cardioplegia in neonatal hearts [13], others have found no significant difference when compared to multidose approaches [14]. It is worth noting that there is significant heterogenity in practice of cardioplegia in pediatric cardiac surgery, as highlighted by a recent survey perfomed in United Kingdom and Ireland [15].

2. Materials and methods

2.1 Literature search strategy

A comprehensive literature search was conducted using various databases, including PubMed, SCOPUS, Embase, Cochrane database, Google scholar and Ovid. The aim was to identify randomised control trials, prospective observational studies, and retrospective analyses that discussed the utilization of myocardial protection methods during pediatric open-heart surgery. The search utilized specific keywords such as ‘pediatric cardiac surgery; cardioplegia, blood cardioplegia, crystalloid cardioplegia, del Nido cardioplegia, Histidine-tryptophan-ketoglutarate cardioplegia, St. Thomas cardioplegia’. These keywords were used both individually and in combination, including Medical Subject Headings terms, to maximise the scope of literature findings. In instances where a paper covered multiple aspects of the myocardial protection, the results were divided and relevant information was included in the respective sections of this review. Only articles written in English were included. Eligible studies for this comprehensive review consisted of pediatric patients undergoing cardiac surgery, involving at least one of the four types of cardioplegia: DN, BC, HTK or St. Thomas.

2.2 Cardioplegic solutions most often used in pediatric cardiac surgery

The original extracellular cardioplegic solution developed by Hearse and colleagues in the early 1970s was known as St. Thomas's Hospital solution No. 1 (STH1) [16]. Over time, this solution underwent refinement and evolved into Plegisol or St. Thomas's Hospital solution No. 2 (STH2) which has become the most widely used crystalloid cardioplegic solution worldwide [17]. One of the main differences between STH1 and STH2 is the inclusion of procaine hydrochloride in STH1, which acts as a membrane stabilizer with known cardioplegic effects [16]. Consequently, patients who receive STH1 may experience fewer reperfusion-induced arrhythmias [18]. Due to the high concentrations of potassium and magnesium concentration in St. Thomas's (STH) cardioplegic solution, it induces rapid cardiac arrest [19]. As a result, repeated perfusion is required during ischemia, typically administered every 20-40 minutes [20]. It is important to note that STH cardioplegia also leads to increased cellular oedema and can damage endothelial function [16].

The Histidine-tryptophan-ketoglutarate (HTK) solution was initially introduced in early 1970s by Hans Jürgen Bretschneider [21]. This crystalloid, intracellular solution with low sodium concentration of 15 mmol/L and extracellular potassium of 9 mmol/L, providing up to 3 hours of myocardial protection with a single dose [21-23]. The reduced sodium level in the extracellular space inhibits the fast inward current and achieves cardiac arrest in diastole. Histidine acts as buffer, supportting anaerobic glycolysis and preventing acidosis [21, 22]. Ketoglurate, an intermediate in the Krebs cycle, enhances ATP production during reperfusion. It also is regulates cell membrane function, reduces reperfusion injury, and decrease edema [24]. However, caution should be exercised when using HTK solution because of its low sodium content, which can effect extracellular sodium levels [25, 26].

In 1990, researchers at the University of Pittsburg developed a long-acting cardioplegia solution specifically designed for pediatric patients, known as del Nido cardioplegia (DNC) [27]. The inclusion of polarizing agents like lidocaine aims to slow down the energy consumption. Additionally, the presence of calcium-competing ions like magnesium in optimum concentration is believed to prevent intracellular calcium accumulation, thus reducing cell injury. The prolonged action of DNC is advantageous in minimizing the detrimental effects of repeated doses of cardioplegia [28]. DNC is an extracellular solution that allows for uninterrupted surgery through a single dosing of cardioplegia. This contributes to reduced surgical times, minimized fluctuations in blood glucose levels, and easier management of glycaemic control [29, 30]. DNC also aids in reducing myocardial oedema, preserving high-energy phosphates and promoting anaerobic glycolysis [30].

3. Results

The initial literature search yielded 1,389 potentially relevant records. Following the screening of titles and abstracts, 141 reports were selected for full-text evaluation. Ultimately, three meta-analysis of randomized clinical studies, consisting of 5 studies [4], 12 studies [46], and 10 studies [51], along with 19 clinical studies [28-45, 47], met predetermined search criteria and were included in this comprehensive review. In total, the analysis encompassed 3,465 pediatric patients who underwent cardiac surgery utilizing various types of cardioplegia.

Changes in cardiac troponin I level (cTnI) (myocardial injury marker) after cardiac surgery. Table 1 presents studies comparing levels of cTnI after different types of cardioplegia. In studies comparing blood cardioplegia (BCP) and cristaloid cardioplegia (STH) [4,31] no significant differences were found in postoperatively cTnI release at 4-6 hours, 12 hours, and 24 hours. A meta-analysis [51], which included 10 eligible studies directly comparing BCP to STH, also showed no significant difference between the two groups, except for significantly lower cTnI levels at 4 hours postoperatively in the BCP group [51].

In a study comparing HTK cardioplegia and cold BCP, it was found that cTnI concentrations were higher in the cold BCP group from postoperative hours 1 to 72 [32]. Another study by Dolcino et al [33] investigated neonates undergoing arterial switch operation with either HTK cardioplegia or warm BCP, and it showed that postoperative troponin concentrations were higher in the HTK group [33]. Studies comparing DNC and BCP [34, 35] concluded that DNC provides lower postoperative troponin I concentration compared to the BCP group. In the study conducted by Panigrahi et al [36] although no significant difference was observed regarding cTnI levels between the two groups, a tendency of greater amount of cTnI release noticed at 12 hours in the BCP group. Two studies [37, 38] comparing HTK cardioplegia and DNC showed that DNC was associated with less release of cTnI.

Data regarding **myocardial metabolism** is limited and is derived from few studies (table 2) which evaluated lactate levels after cardiopulmonary bypass (CPB). According to meta-analysis [4], lactate levels after CPB were significantly lower in the BCP group compared to the CCP group. In the study conducted by Gholampour Dehaki M et al [37] which compared DNC with HTK cardioplegia, lactate levels were significantly higher among patients who received HTK cardioplegia [37].

Cardioplegic solutions effects to myocardial energy marker - ATP level. In the meta-analysis conducted by Mylonas et al. [51], no significant difference between in ATP levels was found between the two groups (BCP vs CCP).

Intraoperative outcomes when using different cardioplegia solutions

Inotropic status after CPB. In a study by Talwar et al. [28], which compared DNC and HTK cardioplegia, DNC was associated with lower inotropic scores compared to HTK cardioplegia. The inotropic score was evaluated at the end of the first 24 hours, after 48 hours, and after 72 hours. Three studies [32,34,36] compared DNC with BCP and concluded that DNC provides lower inotrope scores at 24 hours and at 48 hours [32]. In one study [40], HTK cardioplegia was compared with BCP, and the inotrope score was found to be lower in HTK group. A study comparing DNC vs STH cardioplegia with 220 patiens did not find a significant difference in terms of inotropic score [41]. Additionally, one study [2] analyzed the outcomes between three groups - HTK, cold BCP and STH cardioplegia. It showed that patients who were given HTK solution required a greater need of inotropic support ($P < 0.05$) [2]. Summarized data on inotropic status after CPB is presented in Table 3.

Total volume of cardioplegia. Data comes from two studies [34, 42] which showed that using DNC was associated with lower total volume of cardioplegia (*P*

< 0.001) [34] (331.67±188.07 vs. 458.67±226.62, P=0.022) [42].

Shorter CPB and cross clamp time. Comparing DNC vs BCP [34,42] it was showed that cardiac arrest with DNC was associated with reduced CPB and cross clamp times (P = 0.006 and P = 0.001, respectively) [34]. While other two studies [35,41] found no significant difference regarding CPB and aortic cross-clamp time comparing the same two cardioplegic solutions (P= 0.24). Dolcino et al [33] in their study showed that single-dose HTK may be inadequate for prolonged cross-clamping durations.

Intensive care unit (ICU) stay and hospital stay. According to the meta-analysis [4], which included five studies with a total of 323 patients, there was no significant difference in the length of ICU stay between the BCP and CCP groups. This finding was also confirmed by Mylonas et al. [51] in their meta-analysis, which indicated no significant difference in ICU stay and hospital stay between BCP and CCP groups. In the studies comparing DNC and HTK [28, 37], it was found that DNC was associated with shorter ICU and hospital stay compared to HTK. However, the last meta-analysis [46] did not find significant differences in ICU stay or hospital stay among the four types of cardioplegia (DNC, BCP, HTK, and STH). Additionally, a pairwise meta-analysis of one trial with 101 patients showed that HTK was associated with significantly shorter ICU and hospital stay compared to STH [46]. Summarized data on ICU and hospital stay for different cardioplegic solutions can be found in Table 4.

Low cardiac output syndrome (LCOS). In a retrospective single-centre study [43] involving 1,129 pediatric patients BCP compared to CCP. It was showed that BCP has potential advantages in reducing the incidence of LCOS [43]. Another study comparing DNC vs STH cardioplegia [44] found that DNC was associated with a lower occurrence of LCOS compared to patients who received the standard myocardial protection using a modified STH solution. Additionally, Ebtehal A. Quilsy and colleagues [45] investigated the efficiency of HTK cardioplegia compared to cold BCP and found that HTK was associated with a higher risk of LCOS. Summarized data on LCOS after CPB is presented in table 5.

Resumption of sinus rhythm and postoperative arrythmias. In a comparative study [36] between DNC and BCP, it was found that DNC leads to a faster resumption of spontaneous regular cardiac rhythm (P < 0.0001). Ebtehal A. Quilsy and colleagues [45] examined the efficiency of HTK cardioplegia in comparison with cold BCP. HTK was associated with higher, higher occurrence of postoperative arrhythmias (20% vs 17%).

Postoperative outcomes. The largest mortality data is derived from meta-analysis [51] which found no difference in 30-day mortality when comparing BCP with CCP (OR 1.11, 95% CI 0.43-2.88). In the latest meta-analysis [46] with 1,634 children from 12 studies, outcomes after four types of cardioplegia (DNC, BCP, HTK and STH) were compared and no significant differences in endpoints were observed among the four types of cardioplegia. Floh et al [47] in a retrospective study involving 1534 patients, comparing DNC to BCP, similar mortality rates were found in both groups.

Left and right ventricle functions. Gholampour Dehaki M et al [37] conducted a study comparing the effects of DNC and HTK on peri-operative clinical outcomes in children with Tetralogy of Fallot. They found no significant differences in left ventricular ejection fraction (LV EF) after the surgery. Pérez-Andreu et al [32] showed that LV EF was higher in the

HTK group compared to cold BCP immediately after the operation, at 24 hours and on the first day without inotropic support. However, an experimental animal study [13] found no difference in LV EF at 24 hours post operation or at discharge. The pre-operative right ventricle function, as measured by fractional area change was also similar between BCP and HTK. In a single-center [47], retrospective study which included 1,534 patients undergoing CPB, a significant rise in right ventricular dysfunction was observed in DNC group compared to conventional STH cardioplegia. Summarized data on left and right ventricle functions using different cardioplegic solutions are presented in Table 6.

4. Discussion

This comprehensive review aimed to evaluate the knowledge derived from the randomized and non-randomized studies on myocardial injury, metabolism, energy, intraoperative and postoperative outcomes associated with the use of different cardioplegic solutions in pediatric cardiac surgery. The assessment of myocardial injury, as indicated by cTnI release, focused mainly on the comparison between BCP and CCP, with two meta-analyses involving a total of 8,034 patients showing no significant differences between the two groups. However, there is limited data available comparing HTK and BCP. One study [32] comparing HTK with cold BCP reported more pronounced myocardial damage in the cold BCP group, while another study [33] comparing HTK with warm BCP reported higher troponin concentrations in the HTK group. In comparisons between DNC and BCP, two studies [34, 35] demonstrated lower troponin concentrations in the DNC group. When comparing HTK with DNC [28,37,38], DNC resulted in lower troponin values in multiple studies. It is worth noting that, in the adults, troponin levels at 72 hours have been shown to be a reliable predictor of mid-term mortality [48]. However, there is limited evidence available regarding cTnI measurements after 72 hours specifically in the pediatric population.

In assessing myocardial metabolism through lactate levels, the available data is limited and shows contradictory results. A 2015 meta-analysis [4] indicated that lactate levels are significantly lower in the BCP group, but this finding was primarily influenced by a single study. Another study by Busro et al. [39] did not find a significant difference when comparing BCP and CCP in terms of lactate levels. However, Gholampour Dehaki et al. [37], comparing DNC with CCP, reported significantly higher lactate concentrations in the CCP group, suggesting poorer myocardial metabolism in that group. It is important to note that the available evidence on lactate levels and myocardial metabolism is limited and further research is needed to draw more conclusive findings.

In evaluating the impact of different cardioplegic solutions on myocardial energy resources, several studies have measured ATP levels during BCP and CCP. A meta-analysis published in 2017 [51] examined these data and found no significant difference between the two groups in terms of ATP levels. This suggests that both BCP and CCP are comparable in their ability to maintain myocardial energy resources as measured by ATP levels.

Intraoperative outcomes when using different cardioplegic solutions.

There is limited available data regarding the need for inotropic support when different cardioplegic solutions are used. One study by Talwar et al. [28] compared DNC with HTK and found that the DNC group required less inotropic support. In the comparison between DNC and BCP, data from three studies [32,34,36] favored DNC in terms of reducing the need for inotropes during the first and second postoperative days. However, a study by Elassal et al. [41] comparing DNC and STH found no significant difference in the inotrope status between the two groups.

Regarding the duration of CPB and aortic cross-clamp time, the findings from current studies are contradictory. Two studies [34,42] indicated the superiority of DNC over standard cardioplegia in reducing CPB and aortic cross-clamp time, while two other studies [35,41] found no significant difference between the two cardioplegic solutions in terms of these time parameters.

The length of stay in the ICU was primarily reported based on the actual elapsed time rather than being assessed against specific discharge criteria in the available trials. Additionally, the trials focused on short-term endpoints and did not evaluate long-term functional outcomes [49]. Two meta-analyses comparing BCP with CCP did not find any significant differences in ICU stay. However, when comparing DNC with HTK, two studies reported a shorter duration of ICU stay in the DNC group. Similarly, in the comparisons of DNC with BCP, the DNC group also had a shorter ICU duration according to studies [35, 36, 41].

LCOS is a common complication in children after surgery and is a significant contributor to mortality [50]. A retrospective study conducted at a single center demonstrated that the BCP group had lower rates of LCOS compared to CCP, highlighting the potential advantages of BCP in reducing LCOS occurrence [43]. Similarly, when comparing DNC with the standard STH cardioplegia, a lower incidence of LCOS was observed in the DNC group. Another study conducted by Ebtehal A. Quilsy and colleagues compared HTK cardioplegia with cold BCP and found a higher probability of LCOS when HTK cardioplegia was used [45]. These findings suggest that the choice of cardioplegic solution may have an impact on the occurrence of LCOS in pediatric cardiac surgery.

Postoperative outcomes when using different cardioplegic solutions.

The most recent meta-analysis [46], which included 1,634 children from 12 randomized studies, suggests that there are no significant differences in perioperative mortality among the four types of cardioplegia (DNC, BCP, HTK, and STH) in the pediatric population. However, in adult patients, DNC may be associated with lower perioperative mortality compared to HTK or BCP. Regarding the assessment of left ventricular systolic function before and after surgery using different cardioplegic solutions, current studies do not show significant differences.

In a larger retrospective study [47] involving 1,534 patients, it was found that the DNC group had better postoperative right ventricular function compared to conventional STH cardioplegia. However, it is important to note that the current literature on cardioplegia in children lacks late-phase trials, and the studies conducted so far are of small size and use inconsistent endpoints, providing limited evidence [49].

To thoroughly understand the benefit-risk profiles of different types of cardioplegia in pediatric cardiac surgery, large multicenter randomized studies are needed. These studies will help provide more robust and comprehensive evidence for guiding clinical practice in the field of pediatric cardioplegia.

5. Conclusions

The available studies have not demonstrated any significant mortality benefits comparing the four commonly used cardioplegic solutions (BCP, STH, DNC and HTK) in pediatric cardiac surgery. However, the use of DNC has shown significant benefits in terms of myocardial injury and of other intraoperative variables. Despite these findings, there remains a substantial need for well-designed multicenter randomized controlled trials to establish clear evidence for myocardial protection in pediatric cardiac surgery.

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Table 1. Changes in cardiac troponin I level after cardiopulmonary bypass

Authors	Study type	Patient number, n	Type of cardioplegia used	P-value at 4-6 hours	P-value at 8 hours	P value at 12 hours	P value at 24 hours	P value at 48 hours	P value at 72 hours	When study performed, year
Fang et al. [4]	Meta-analysis	323	BCP vs CCP	P=0.09	-	P=0.53	P=0.12	-	-	2014
Romolo et al. [31]	Randomized clinical trial	70	BCP vs STH	-	-	-	-	-	-	2016-2017
Mylonas et al. [51]	Meta-analysis	697	BCP vs STH	P=0.860	-	P=0.019	P=0.000	-	-	2017
Pérez-Andreu et al. [32]	Observational	64	Cold BCP vs HTK	P=0.001	-	P<0.001	P<0.001	P=0.001	P=0.003	2010-2015; 2016-2018
Dolcino et al. [33]	Observational	101	Warm BCP vs HTK	-	-	-	-	P<0.001	-	2014-2016
Isildak et al. [34]	Randomized clinical trial	80	BCP vs DNC	P=0.091	-	-	P=0.045	P=0.315	-	2021
Haranal et al. [35]	Randomized clinical trial	100	BCP vs BSTH (blood-based STH)	-	-	-	P=0.629	-	-	2018-2019
Panigrahi et al. [36]	Randomized clinical trial	60	BCP vs DNC	P=0.873	-	P=0.180	P=0.780	-	-	2018
Dehaki et al. [37]	Randomized clinical trial	40	HTK vs DNC	P<0.001	-	-	-	-	-	2018
Tunçer et al. [38]	Observational	27	HTK vs DNC	-	P=0.016	-	-	-	-	2017-2018

Table 2. *Lactate levels after cardiopulmonary bypass*

Authors	Study type	Patient number, n	Type of cardioplegia used	P value	When study was performed (year)
Fang et al [4]	Meta-analysis	323	BCP vs CCP	P=0.03	2014
Gholampour Dehaki M et al [37]	Randomized clinical trial	40	DNC vs HTK	P=0.001	2018

Table 3. *Inotropic status after CPB.*

Authors	Study type	Patient number, n	Type of cardioplegia used	P-value at 0 hours	P-value at 24 hours	P value at 48 hours	P value at 72 hours	P value at 96 hours	P-value at 120 hours	When study performed, year
Talvar et al [28]	Randomized clinical trial	100	DNC vs HTK	-	P=0.021	P=0.036	P=0.026	P=0.008	-	2017-2018
Pérez-Andreu et al [32]	Observational	64	Cold BCP vs HTK	P=0.001	P=0.006	P=0.059	P=0.285	P=0.658	P=0.924	2010-2015; 2016-2018
Isildak et al [34]	Randomized clinical trial	80	BCP vs DNC	P=0.058	P=0.032	P=0.005	P=0.136	-	-	2021
Panigrahi et al [36]	Randomized clinical trial	60	BCP vs DNC	P=0.040	P=0.030	P=0.610	P=0.350	-	-	2018
Bibevski et al [40]	Observational	132	cold BCP vs HTK	P<0.05						2007-201
Elassal et al [41]	Observational	220	DNC vs STH	P=0.591						2011-2019
Hamed et al [2]	Randomized clinical trial	60	HTK vs cold BCP vs STH	P<0.05						2015-2017

Table 4. *Intensive care unit and hospital stay after CPB in pediatric patients.*

Authors	Study type	Patient number, n	Type of cardioplegia used	ICU length of stay, P value	Hospital length of stay, P value	When study performed, year
Fang et al [4]	Meta-analysis	323	BCP vs CCP	P=0.25	-	2014
Mylonas et al [51]	Meta-analysis	697	BCP vs STH	P=0.002	P=0.060	2017
Talvar et al [28]	Randomized clinical trial	100	DNC vs HTK	P=0.05	P<0.001	2017-2018
Dehaki et al [37]	Randomized clinical trial	40	DNC vs HTK	P=0.02	-	2018
Tan et al [46]	Meta-analysis	101	HTK vs STH	-	-	2022

Table 5. *Low cardiac output syndrome (LCOS) after CPB using different cardioplegic solutions*

Authors	Study type	Patient number, n	Type of cardioplegia used	P value	When study performed, year
Sobieraj et al [43]	Observational	1129	BCP vs CCP	P = 0.0017	2006-2012
Caneo et al [44]	Observational	500	DNC vs STH	P⩽ 0.05	2015-2019
Qulisy et al [45]	Observational	154	HTK vs cold BCP	P=0.14	2013-2014

Table 6. Left ventricle (LV) and right ventricle (RV) function after CPB when different cardioplegic solutions were used.

Authors	**Study type**	**Patient num-ber, n**	**Type of cardioplegia used**	**Pre-operative P-value (LV)**	**Intraoperative P-value (LV)**	**P-value after the surgery (LV)**	**P value at 24 hours (LV)**	**P value the first day without inotropic support (LV)**	**P value at discharge (LV)**	**Intraoperative P-value (RV)**	**P value of at discharge (RV)**	**When study performed, year**
Dehaki et al [37]	Randomized clinical trial	40	DNC vs HTK	P=0.791	-	P=0.750	-	-	P=0.906	-	-	2018
Pérez-Andreu et al [32]	Observational	64	Cold BCP vs HTK	P=0.880	-	P=0.005	P=0.001	P=0.011		-	-	2010-2015; 2016-2018
Floh et al [47]	Observational	1534	DNC vs STH	-	P=0.90	-	-	-	P=0.43	<0.001	P<0.001	2013-2016