

The Efficacy of Resin Hemoperfusion Cartridge on Inflammatory Responses during Adult Cardiopulmonary Bypass

Zijian He^a Hongyu Lu^a Xuhua Jian^a Guanhua Li^b Dengke Xiao^a
Qingqing Meng^a Jimei Chen^a Chengbin Zhou^a

^aDepartment of Cardiovascular Surgery, Guangdong Provincial Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China; ^bDepartment of Cardiovascular Surgery, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China

Keywords

Surgical valve replacement · Cardiopulmonary bypass · Systemic inflammatory responses · Hemoperfusion cartridge · Adsorption

Abstract

Aim: This study aimed to evaluate the efficacy of the resin hemoperfusion device (HA380 hemoperfusion cartridge) on inflammatory responses during adult cardiopulmonary bypass (CPB). **Methods:** Sixty patients undergoing surgical valve replacement were randomized into the HP group ($n = 30$) with an HA380 hemoperfusion cartridge in the CPB circuit or the control group ($n = 30$) with the conventional CPB circuit. The results of routine blood tests, blood biochemical indexes, and inflammatory factors were analyzed at V0 (pre-CPB), V1 (CPB 30 min), V2 (ICU 0 h), V3 (ICU 6 h), and V4 (ICU 24 h). **Results:** The HP group had significantly lower levels of IL-6, IL-8, and IL-10. Significant estimation of group differences in the generalized estimating equation (GEE) models was also observed in IL-6 and IL-10. The HP group had significantly lower levels of creatinine (Cr), aminotransferase (AST), and total bilirubin (TBil) compared to the control group. The estimation of differences of Cr, AST, and TBil all

reached statistical significance in GEE results. The HP group had significantly less vasopressor requirement and shorter mechanical ventilation time and ICU stay time as compared to the control group. **Conclusion:** The HA380 hemoperfusion cartridge could effectively reduce the systemic inflammatory responses and improve postoperative recovery of patients during adult CPB.

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Introduction

Cardiopulmonary bypass (CPB) temporarily takes over the function of the heart and lungs by diverting blood through a heart-lung machine to maintain the circulation and the oxygen content of the body [1], allowing to perform open-heart surgery in the bloodless and even motionless heart [2]. However, CPB has been shown with systematic inflammatory responses due to traumatic stress and activations of monocyte/macrophage and coagulation [3, 4]. During CPB, the release of several inflammatory molecules (C3a, C5a, histamine, IL-6, IL-8, and TNF- α) causes activation of cellular responses, in turn leading to systemic inflammation, increased vascu-

lar permeability, and thrombosis [5]. The CPB-induced systemic inflammation has been shown to induce adverse effects, such as hemodynamic instability, coagulopathy, acute organs injury, and even death [6–10].

Given the association between elevated proinflammatory cytokine levels and adverse clinical outcomes [11], it has been hypothesized that extracorporeal removal of inflammatory cytokines may improve the prognosis of patients receiving CPB [12]. A variety of strategies have been developed to reduce the systemic inflammatory responses during CPB, including pharmaceutical (such as steroidal and nonsteroidal anti-inflammatories, complement inhibitors, protease inhibitors, and antioxidants) and nonpharmaceutical (such as removal of the inflammatory molecules by hemoperfusion, reducing surface area by minimizing circuits, and improving the biocompatibility of extracorporeal surfaces) approaches [3, 13]. However, Clive Landis et al. [3] reported that about one-third of these strategies exhibit clinically improved efficacy. Thus, it is still urgent to develop a novel strategy to reduce CPB-induced systemic inflammation.

The HA380 hemoperfusion cartridge contains biocompatible neutral macroporous adsorption resin made of coated polystyrene, which is capable of removing circulating molecules ranging from 10 to 60 kDa at molecular weight [14]. The HA series hemoperfusion cartridges have been applied to extracorporeal blood purification treatments in several severe diseases, such as multiple organ dysfunction syndrome, sepsis, severe acute pancreatitis, and COVID-19 [15–19]. The HA series hemoperfusion cartridges can not only significantly reduce the levels of inflammatory factors, such as IL-6, IL-10, and TNF- α , and correct the imbalance of inflammatory factors, but also improve the patient's hemodynamics, reduce the use of vasopressors, shorten the patient's hospital stay, and improve patient prognosis [15–18]. However, the HA series hemoperfusion cartridges have not been used during CPB. Therefore, the purpose of this study was to evaluate the efficacy of the HA380 hemoperfusion cartridge on eliminating inflammatory factors during CPB in cardiac surgeries.

Methods

Study Subjects

From February 2018 to February 2019, 60 patients undergoing surgical valve replacement in Guangdong Provincial People's Hospital were enrolled and randomized into the control group ($n = 30$) receiving conventional CPB or the HP group ($n = 30$) undergoing CPB plus HA380 cartridge hemoperfusion. The inclusion criteria

were (1) rheumatic heart valve disease as the primary diagnosis; (2) preoperative cardiac function from NYHA II–III; (3) cardiothoracic ratio ≤ 0.7 by chest film; (4) combined with one of the following diseases: liver injury (grade 1–3) or kidney injury (CKD stage 0–2); and (5) all patients underwent combined valve replacement and the CPB time > 2 h. The exclusion criteria were age over 75, emergency surgery, redo cardiac surgery, pregnancy, and clinically or laboratory apparent infection.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethical Review Board of Guangdong Provincial People's Hospital. Written informed consent was obtained from each patient.

CPB Treatment plus HA380 Hemoperfusion Cartridge

Patients in both groups were anesthetized with midazolam, etomidate, rocuronium, and sufentanil, and propofol and cisatracurium, remifentanyl, and combined inhalation of sevoflurane were used to maintain anesthesia. The Stöckert S3 Heart-lung Machine (Stöckert, Munich, Germany) and Medtronic Affinity NT Oxygenator (Medtronic Inc., Minneapolis, MN, USA) were used for CPB. The CPB circuit was primed with 1,500 mL of lactated Ringer's solution and 50 mg of heparin, and 4 mg/kg heparin was administered for systemic anticoagulation. The blood perfusion flow was 60–80 mL/kg/min. Intraoperative systolic pressure was maintained from 50 to 80 mm Hg, and hematocrit was maintained at 22–30% with activated clotting time above 480 s. During CPB weaning off, protamine was used to neutralize with heparin. In the HP group, the CPB circuit was connected to a HA380 hemoperfusion cartridge (Jafron Biomedical Co., Zhuhai, China). Blood flow through the HA380 cartridge was set at a rate of 200–300 mL/min, and the perfusion time was the same as CPB time. HA380 hemoperfusion cartridge was not used in the control group.

Assay of Serum Levels of Cytokines and Blood Biochemical Data

Blood samples were collected at V0 (pre-CPB), V1 (CPB 30 min), V2 (ICU 0 h), V3 (ICU 6 h), and V4 (ICU 24 h) and were immediately centrifuged at 1,500 g for 10 min. The resulting plasma was stored at 4°C. The concentration of TNF- α was detected by radioimmunoassay using a γ radioimmunocounter CG 1500 (Zhongke Zhongjia, China), and the levels of IL-6 and IL-10 were detected by the IMMULITE[®] 1000 kit using chemiluminescent technology (Siemens, Munich, Germany) according to the manufacturer's protocols. Serum levels of creatinine (Cr), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were determined by using the Beckman AU5800 biochemical analyzer (USA) using the colorimetric method. Blood lactate was tested by using the IL GEM Premier 3000 blood gas analyzer (USA).

International normalized ratio was determined by using STA-R Coagulation Analyzers (Diagnostica Stago S.A.S, Asnières sur Seine, France). Total bilirubin (TBil) was assessed by using a Cobas[®] 8000 modular analyzer (Roche Cobas 8000, c702; Roche Diagnostics, Basel, Switzerland). The platelet counts were detected by using a Sysmex XN-9000 analyzer (Sysmex, Hyogo, Japan).

Statistical Analysis

Continuous data were expressed with mean \pm standard deviation while categorical data were displayed with number and percentage (%). For comparison means between control and HP groups, the Student's independent t test was used; if normality was

Table 1. Patients' demographic and clinical characteristics

Parameters	Control (<i>n</i> = 30)	HP (<i>n</i> = 30)	<i>p</i> value
Gender, <i>n</i> (%)			
Male	18 (60.00)	14 (46.67)	0.301
Female	12 (40.00)	16 (53.33)	
Age, years	55.43±9.90	54.37±9.53	0.672
Weight, kg	58.82±11.39	55.70±8.95	0.243
Surgical procedures, <i>n</i> (%)			
Aortic and mitral valve replacement	30 (100.00)	30 (100.00)	1.000
Tricuspid valve repair	22 (73.33)	29 (96.67)	
Atrial fibrillation radiofrequency ablation	2 (6.67)	3 (10.00)	
Left atrial plication	1 (3.33)	1 (3.33)	
Preoperative LVEF	58.00±4.64	58.17±5.36	0.898
CPB time, min	159.43±34.19	155.87±30.24	0.670
Cross-clamp time, min	103.43±20.87	99.87±34.70	0.631

LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass.

Table 2. Patients' ICU outcomes

Parameters	Control (<i>n</i> = 30)	HP (<i>n</i> = 30)	<i>p</i> value
MV time, h	25.10±15.78	16.17±6.42	0.007
Postoperative 24-h urine output, mL	2,572.00±849.11	2,613.17±572.17	0.826
Postoperative 24-h pleural effusion, mL	297.67±108.17	256.00±102.94	0.132
ICU time, h	73.28±52.56	34.40±20.06	<0.001
Maximum VIS in the first postoperative 24 h	13.26±18.09	4.17±2.89	0.006

VIS was calculated by the following equation using drug dosage in µg/kg/min: (dopamine + dobutamine) + (milrinone × 10) + (epinephrine × 100) + (norepinephrine × 100). MV, mechanical ventilation; ICU, intensive care unit; VIS, vasoactive inotropic score.

not assumed, the Mann-Whitney U test would be used instead. A χ^2 test was used to test the difference in the distribution of categorical data between 2 groups. Two-way mixed-design ANOVA and Fisher's LSD as post hoc comparisons were used to compare the differences between groups and among time points. To further investigate the association between group variable and outcome index, a linear regression under a generalized estimating equation (GEE) model was used. All patients' results were measured at 5 time points: V0 (pre-CPB), V1 (CPB 30 min), V2 (ICU 0 h), V3 (ICU 6 h), and V4 (ICU 24 h). An AR(1) correlation matrix was adopted for the repeated measure data. A two-tailed *p* value below 0.05 is recognized as statistically significant of each test. All analyses were performed using IBM SPSS Version 25.0 (SPSS Statistics V25; IBM Corporation, Somers, NY, USA).

Results

Patients' Demographic and Clinical Characteristics

A total of 60 patients 54.90 ± 9.65 years old were included and randomized into the control group and the

HP group (*n* = 30 for each group). There was no significant difference in baseline characteristics between the 2 groups, including gender, age, and weight (Table 1). All patients underwent aortic and mitral valve replacement, and some patients underwent tricuspid annuloplasty, atrial fibrillation radiofrequency ablation, and left atrial plication. There was no difference with regard to surgical procedures, preoperative LVEF, CPB time, and aortic cross-clamping time between the 2 groups (Table 1).

ICU Outcomes

As shown in Table 2, there were no significant differences in postoperative 24-h urine output and the occurrence of pleural effusion between the 2 groups (*p* > 0.05). Neither severe complications nor in-hospital deaths occurred in both groups. The HP group had significantly shorter mechanical ventilation (MV) time (16.17 ± 6.42 vs. 25.10 ± 15.78, *p* < 0.01) and ICU stay time (34.40 ± 20.06 vs. 73.28 ± 52.56, *p* < 0.01) as compared with the

Table 3. The results of vital signs, blood count, inflammatory factors, and hepatic and renal function between the control and HP groups

Parameters	Control group (n = 30)						HP group (n = 30)						GEE regression		p value
	V0 (pre-CPB)	V1 (CPB 30 min)	V2 (ICU 0 h)	V3 (ICU 6 h)	V4 (ICU 24 h)		V0 (pre-CPB)	V1 (CPB 30 min)	V2 (ICU 0 h)	V3 (ICU 6 h)	V4 (ICU 24 h)		B (95% CI)		
MAP, mm Hg	96.54±11.21	65.73±6.25	87.80±9.20	94.52±10.00	100.06±7.66		90.17±12.72*	67.67±6.80	87.81±8.63	89.00±8.71*	94.76±9.17*		-2.95 (-5.29 to -0.62)		0.013
INR	1.17±0.32	-	1.40±0.28	-	1.27±0.14		1.11±0.25	-	1.40±0.15	-	1.30±0.15		-0.01 (-0.10 to 0.08)		0.807
PLT, 10 ⁹ /L	207.87±73.65	-	132.90±47.54	-	135.47±52.25		212.83±45.23	-	132.63±30.55	-	147.17±40.30		6.05 (-15.61 to 27.70)		0.584
TNF-α, pg/mL	11.55±6.14	16.22±26.12	30.10±48.07	17.60±18.28	10.24±5.30		12.99±6.20	11.93±5.51	15.23±6.42	14.31±6.53	11.45±5.19		-2.23 (-6.71 to 2.24)		0.328
IL-6, pg/mL	6.30±9.87	9.15±14.90	195.64±258.95	469.37±333.43	126.91±79.79		5.88±10.73	4.70±3.62	56.65±46.35*	204.81±140.52*	89.33±62.16		-82.15 (-117.69 to -46.62)		<0.001
IL-8, pg/mL	29.10±56.84	20.80±24.63	204.33±383.18	91.28±90.24	38.32±30.87		86.63±255.39	15.27±15.06	94.88±161.42	39.88±22.72*	28.73±23.89		-22.18 (-61.24 to 16.89)		0.266
IL-10, pg/mL	5.00±0.00	47.90±79.46	289.18±317.70	55.97±86.95	9.27±7.20		16.20±52.65	25.64±30.69	81.25±93.92*	15.03±15.55	9.37±6.34		-48.90 (-77.48 to -20.33)		<0.001
Cr, μmol/L	76.83±15.53	-	92.46±29.22	-	99.40±27.65		69.08±16.22	-	71.13±13.16*	-	80.19±26.54*		-14.93 (-24.41 to -5.45)		0.002
AST, U/L	26.17±9.90	-	80.23±58.40	-	97.90±83.39		23.20±7.63	-	62.07±27.19	-	56.83±28.67*		-21.18 (-38.07 to -4.28)		0.014
ALT, U/L	23.20±13.40	-	38.93±29.89	-	32.20±27.68		19.43±9.93	-	24.83±12.86	-	21.77±9.48		-8.50 (-15.54 to -1.46)		0.018
TBil, μmol/L	16.89±7.09	-	25.50±15.16	-	24.59±15.74		15.24±7.81	-	19.21±11.79*	-	16.12±7.27*		-5.23 (-9.82 to -0.64)		0.026
LAC, mmol/L	1.09±0.54	1.78±0.78	3.06±1.95	5.59±3.24	3.08±2.21		1.34±0.69	1.87±0.69	2.59±0.91	3.96±2.05	2.14±1.16		-0.50 (-1.00 to 0.00)		0.050

GEE, generalized estimating equation; MAP, mean arterial pressure; PLT, platelet; INR, international normalized ratio; Cr, creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; Lac, lactate. * $p < 0.05$ compared to the control group.

control group. The control group had higher maximum vasoactive inotropic score in the first 24 h postoperative as compared with the HP group (13.26 ± 18.09 vs. 4.17 ± 2.89 , $p < 0.01$).

Hemodynamics and Blood Biochemical Data

Hemodynamic parameters and the estimations of group differences are displayed in Table 3. There were no differences in mean arterial pressure (MAP) among all time points between the 2 groups. In both groups, the MAP decreased at V1 but increased at V2, V3, and V4, which was related to the CPB and cardiac procedures. However, there was a significant difference in the estimation of GEE linear regression models, indicating that the MAP was significantly different between the 2 groups.

In both the comparison between 2 groups across time and the estimation in GEE models (Table 3), there were no significant differences in the levels of international normalized ratio and platelet between the 2 groups (all $p > 0.05$). However, the HP group had significantly lower levels of Cr, AST, and TBil at V2 and V4 than that of the control group. The estimation of differences of Cr, AST, ALT, and TBil all reached statistical difference in GEE results. These results indicated that the HP group may have better hepatic and renal functions after CPB. There were no significant differences in the levels of lactate acid between the 2 groups ($p > 0.05$).

Inflammatory Factors

The HP group had significantly lower levels of IL-6, IL-8, and IL-10 as compared with the control group (Table 3). A significant estimation of group difference in GEE models was also observed in IL-6 and IL-10. The trend and levels of inflammatory factors (TNF-α, IL-6, IL-8, and IL-10) across time are compared in Figure 1. It was found that all inflammatory factors during CPB increased from V1 to V2 (to V3 for IL-6) and then reduced to the normal range at V4. Overall, the levels of all inflammatory factors were significantly or descriptively lower in the HP group than that in the control group.

Discussion

The HA series hemoperfusion cartridges have been applied to extracorporeal blood purification treatments in several severe diseases [15–19] but have not been used during CPB in cardiac surgery. The HA380 hemoperfusion cartridge is designed for extracorporeal blood purification treatments for critically ill patients suffered from

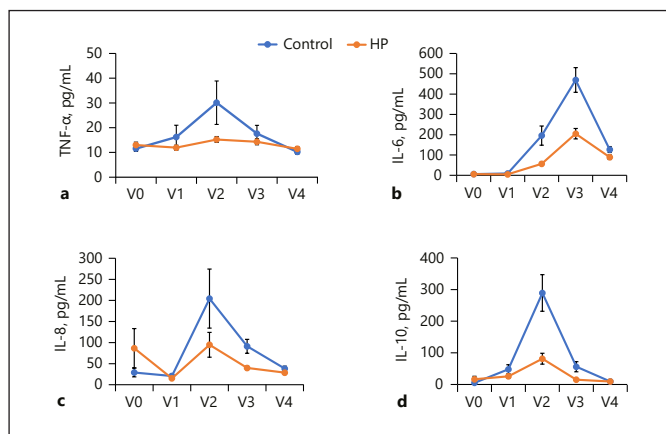


Fig. 1. The changes of the mean across time of inflammatory factors, including TNF- α (a), IL-6 (b), IL-8 (c), and IL-10 (d). Error bars are standard error.

cytokine storm, such as sepsis, pancreatitis, trauma, cardiac surgery, and severe inflammation [14]. The resin pore size ranges of HA380 are 500 Da–60 kDa [14]. In this study, we conducted a pilot randomized controlled trial to evaluate the efficacy of the HA380 hemoperfusion cartridge on eliminating inflammatory factors during CPB. The results showed that the HP group had significantly less vasopressor requirement (indicated by vasoactive inotropic score) and shorter MV time and ICU stay time as compared to the control group. The HP group had significantly lower levels of IL-6 (V2 and V3), IL-8 (V3), and IL-10 (V2) as compared with the control group. A significant estimation of group difference in GEE models was also observed in IL-6 and IL-10. The HP group had significantly lower levels of Cr, AST, and TBil at V2 and V4. The estimation of differences of Cr, AST, ALT, and TBil all reached statistical significance in GEE results. These results indicated that the HP group may have better hepatic and renal functions after CPB.

In this study, the research was referred to the design of a hemoperfusion cartridge for eliminating inflammatory factors [20–24]. Our results showed that the HA380 hemoperfusion cartridge exhibited good efficacy on the absorption of inflammatory factors and the postoperative recovery of patients, which is consistent with the results of previous studies [20–22]. In a series of 16 cardiac surgery patients with post-CPB systemic inflammatory response syndrome and subsequent acute kidney injury, Träger et al. [22] reported that hemoperfusion treatment can reduce the elevated cytokine (IL-6 and IL-8) levels, stabilize the deranged hemodynamic, and improve organ

function. In another series of 39 cardiac surgery patients with acute infective endocarditis receiving valve replacement during CPB, Träger et al. [21] also reported that hemoperfusion treatment can decrease the postoperative response of key cytokines, clinical metabolic parameters, and the need for vasopressors, improving hemodynamic stability and organ function. Likewise, Nemeth et al. [20] had demonstrated that intraoperative hemoperfusion treatment was associated with reduced vasopressor demand in patients undergoing CPB orthotopic heart transplantation. In addition, the durations of MV, ICU stay, and renal replacement therapy were shortened [20], which is in line with our observations. Nevertheless, the conflicting findings of 2 pilot randomized controlled trials should be noted that hemoperfusion treatment during CPB did not lead to a decrease in perioperative cytokine levels nor any improvement in clinical outcomes [23, 24]. Thus, a large prospective trial should be conducted to further evaluate the efficacy of the HA380 hemoperfusion cartridge during CPB in cardiac surgery.

Compared to the “membrane-based” blood purification techniques, the surface area contacting with blood components in the adsorption techniques (such as the HA series hemoperfusion cartridges) is much larger [25]. Therefore, biocompatibility is particularly important for hemoperfusion cartridges. In vitro testing has suggested that HA cartridges have an optimal level of biocompatibility and are not associated with adverse effects nor cytotoxicity during hemoperfusion [14]. The HA series hemoperfusion cartridges have been widely used in China, and only a few incidents of fever and transient thrombocytopenia have been reported [18, 26]. In this study, neither fever nor thrombocytopenia was observed in the HP group. These results suggest that the HA380 cartridges are biocompatible and safe for hemoperfusion during CPB in cardiac surgery.

There are still some limitations in this study. First, the sample size of this study was relatively small. In addition, we did not determine the full panel of proinflammatory and anti-inflammatory cytokines. Large prospective trials should be conducted to validate the findings of this study. In summary, our results demonstrated that the HA380 hemoperfusion cartridge can effectively reduce the intraoperative levels of inflammatory factors, decrease vasopressor requirement, shorten postoperative MV time and ICU stay time, and improve hepatic and renal functions as compared with the control group, indicating reduction in systemic inflammatory response and improvement of postoperative recovery in patients receiving CPB.

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Statement of Ethics

This research was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committees of Guangdong Provincial People's Hospital. Each recruited patient provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Chengbin Zhou and Zijian He designed the experiments. Zijian He, Hongyu Lu, Xuhua Jian, Dengke Xiao, Qingqing Meng, and Jimei Chen performed the experiments. Guanhua Li analyzed the experimental results. Zijian He wrote the manuscript.

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