Effect of Blood Hemoperfusion Therapy in Acute Type A Aortic Dissection Surgery：a retrospective observational study

Juxiang Wang (xmwjx2012@126.com)
Cardiovascular Hospital of Xiamen University School of Medicine Xiamen University Xiamen Fujian
Bin Chen
Xiamen Port Clinic of Xiamen Customs
Junhao Xie
Cardiovascular Hospital of Xiamen University School of Medicine Xiamen University Xiamen Fujian
Huilong Chen
Cardiovascular Hospital of Xiamen University School of Medicine Xiamen University Xiamen Fujian
Lihua Li
Cardiovascular Hospital of Xiamen University School of Medicine Xiamen University Xiamen Fujian
Weiqun Zhang
Cardiovascular Hospital of Xiamen University School of Medicine Xiamen University Xiamen Fujian
Lin Lu
Cardiovascular Hospital of Xiamen University School of Medicine Xiamen University Xiamen Fujian
Xijie Wu
Cardiovascular Hospital of Xiamen University School of Medicine Xiamen University Xiamen Fujian

Research Article

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Abstract

Background

Although hemoperfusion is considered an efficient technique of removal specific solutes in inflammatory states, there is no established indications for triggered treatment. This study aimed to evaluate whether the adding of a new hemoperfusion cartridge (HA-380) in cardiopulmonary bypass (CPB) circuit of acute type A aortic dissection (ATAAD) surgery is associated with an attenuation of inflammatory response and improvement in organ function.

Methods

A retrospective observational cohort study was conducted on patients with ATAAD undergoing central repair between March 2021 and February 2022 at a Regional Medical Center Hospital of Southeast China. Patients received regular CPB during operation in the first 8 months (first half of the period) and received HA-380 cartridge adding in CPB circuit in the rest 8 months (second half). Patients were received intensive care therapy in a cardiac surgery intensive care unit (ICU) postoperatively. The primary outcomes were interleukin-6 (IL-6) levels during the perioperative period. The secondary outcomes were major complications included postoperative acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS).

Results

Among the 173 ATAAD patients received central repair during the study period, 121 patients fulfilled the eligibility criteria, with 59 patients in the CON group and 62 patients in the HP group. Disease severity was similar between the two groups. The serum IL-6 values were increased rapidly postoperatively compared symptom onset and were lower in HP group than in CON group (146.13pg/ml vs. 205.73pg/ml, *P = 0.020*). The incidence of postoperative AKI and severe ARDS were lower in HP group (25.4% vs. 44.6%, *P = 0.001*), and (18.3% vs. 35.1%, *P = 0.04*). The incidence rate ratio (RR) for AKI and severe ARDS were 0.57 (95% CI 0.35–0.79; *p = 0.012*) and 0.52 (95% CI 0.28–0.92; *p = 0.043*) in HP group compared to CON group.

Conclusions

The use of HA380 to CPB circuit was associated with significantly attenuated IL-6 level and reduced major complications, AKI and severe ARDS after ATAAD surgery.

Background

Hemoperfusion, a third mechanism of extracorporeal blood purification with different mechanism from diffusion and convection, means removal of plasma solute by a cartridge containing a solid agent as charcoal or resins [1].It can remove specific toxins and solutes in severe inflammatory states and related disorders[2]. Jafron HA cartridges series (Jafron Biomedical, Guangdong, China), one of the sorbent technologies with an optimal level of biocompatibility and noserious adverse reactions[3], has been used in some critical inflammatory response setting[4] and in cardiac surgery[5].

Although there is no sufficient evidence to support the applying hemoperfusion to improve survival in sepsis[6]. Part of the reason is that the optimal timing, dose and duration of hemoperfusion [7] were not clear and also including endotoxin adsorptions [8].Contrary to sepsis is a continuous and amplifying disorder process [6], cardiac surgery is an aseptic process and the level of systemic inflammatory response would down-regulate after surgery[5]. Because of the single peak of inflammatory response and injury, hemoperfusion therapy may attenuate it and bring beneficial effects. But a previous study showed that the use of a CytoSorb® filter (one of the hemoperfusion cartridges) during cardiopulmonary bypass (CPB) was not associated with a decrease in inflammatory cytokines or an improvement in relevant outcomes after cardiac surgery[9].A relatively low cytokine levels and a lower rate of complications might explain why relevant outcome benefits were not found.

Different from the elective cardiac surgery, acute type A aortic dissection (ATAAD) is a life-threatening medical emergency and immediate surgery is an effective treatment [10]. An emergent surgery of ATAAD is a complex procedure with prolonged CPB and operation time and required deep hypothermic circulatory arrest. All above associate with a more severe inflammatory response than less complex cardiac surgery [11–13] and postoperative complications exhibit high morbidity and poor prognosis [14]. In order to reduce the postoperative complications, as acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS), and mortality, we hypothesized that placement of a hemoperfusion cartridge in the CPB circuit could reduce the levels of cytokines and benefit outcomes in patients undergoing emergent operation of ATAAD and that had not been reported before. For the above reasons, we conducted this retrospective cohort analysis of adding a hemoperfusion cartridge HA-380(one of Jafron HA cartridges series) in CPB circuit to evaluate the effect of the technology on ATAAD surgery management.

Methods

Study design

The study was followed in accordance with the ethics committee of the Xiamen Cardiovascular Hospital of Xiamen University and with the Helsinki Declaration of 1975 (Study title: The study of adding a resin hemoperfusion therapy in CPB during central repair of acute type A aortic dissection, ethics approval number: XXY-AF/EC-09.01/2.0).Written informed consent to participate in the study and consent to publish was obtained from each patient. From 1st March, 2021 to 28th February, 2022, 173 ATAAD patients undergoing open repair surgery were screened. Among them, 121 patients fulfilled the inclusion

criteria, and 52 did not. Before 31st August, 2021, 59 patients received conventional CPB without a hemoperfusion cartridge as CON group and after 1st September, 62 patients received CPB with the HA380 cartridge as HP group. A diagram of patient inclusion was shown in Fig. 1.

Inclusion criteria were not less than 18 years age, with time from ATAAD symptom onset to operating room ≤ 72hours and aortic arch involvement. Exclusion criteria were 1) hereditary connective tissue diseases such as Marfan syndrome; 2) did not receive prophylactical methylprednisolone for it can affect inflammatory mediators[15]; 3) platelet(PLT)count less than 100×10^9/L before operation[16]; 4) did not receive hypothermic circulatory arrest and total arch replacement operation. Moreover, 4 patients additionally excluded who died within the first postoperative week (2 in each group). Cause of death was dissection-related malperfusion syndrome in cardiac and brain system [17] that could not be rescued by hemoperfusion. Thus, a total of 117 patients, 60 in HP group and 57 in CON group, were included in the pooled analysis as shown in Fig. 1.

Medical therapy and surgical Procedure

Clinical findings were correlated with computed tomography angiography to diagnose ATAAD including pericardial tamponade, aortic regurgitation, dissected branch vessels and shock. The initial medical therapy included β-blockers, calcium channel blockers, and analgesics with same treatment principles.

All patients received a median sternotomy and CPB with selective antegrade cerebral perfusion. Methylprednisolone, 500 mg was administered at CPB initiated. Circulatory arrest was initiated when the nasopharyngeal temperature reached to 25°C, and right axillary or bilateral axillary artery cannulation was used for selective antegrade cerebral perfusion. Aortic root procedures, Bentall, David, aortic valve replacement/repair, or coronary artery bypass graft, were performed if indicated and ascending aorta were replacement. A 4-branch prosthetic graft (InterVascular SAS, France) were used for total arch replacement combined with an elephant trunk stent (Shanghai MicroPort Endovascular MedTech Co., Ltd, Shanghai, China) implanted into the true lumen of the distal aorta. Interventions of the distal aorta with an endovascular stent were combined with or followed the open procedure, depending on the dissection. Patients were received intensive care therapy in an intensive care unit (ICU) by the same team of doctors and nurses postoperatively.

CPB plus HA380 cartridge

All patients were anesthetized with midazolam, etomidate, propofol, sufentanil, and rocuronium. An S5 Heart-Lung Machine (Stockert Instrumente GmbH, Germany) and Medtronic Affinity NT Oxygenator (Medtronic Inc., Minneapolis, MN, USA) were used for CPB. Blood perfusion flow was 60–80 ml/kg/min and intraoperative mean arterial pressure was maintained at 50 to 80 mmHg. Activated clotting time maintained above 480s by heparin and protamine.

In HP group, a HA-380 hemoperfusion cartridge (Jafron Biomedical Co., Zhuhai, China) was placed in a side-circuit connected between the oxygenator and venous reservoir prior to the start of the CPB. Blood flow through the HA380 cartridge was set at a rate of 200–300 ml/min. Flow through the cartridge was

suspended during cardiac arrest. No extra anticoagulation was used in the hemoperfusion and no clotting was observed. The HA380 cartridge was not used in CON group.

Cytokine level and blood biochemical analysis

Interleukin-6 (IL-6) levels were measured with a UniCel DxI 800 Access Immunoassay System (Chaska, MN, USA) preoperative, immediately postoperative, and on postoperative day 1 and day 2. Blood gas analysis and measurement of lactate were performed using a Radiometer ABL90 Flex (Radiometer Medical, Denmark). Other laboratory tests including liver and kidney function, coagulation function, myocardial markers, and infection-related indices were tested routinely.

End points

The primary outcomes were postoperative cytokine levels as IL-6. Key secondary outcomes were major complications included postoperative AKI and dependence on renal replacement therapy, severe ARDS and the duration of mechanical ventilation. Additional secondary outcomes included reintubation and tracheotomy, delirium and stroke, paraplegia, the length of ICU and hospital stay, and in-hospital mortality. Postoperative AKI during the first week after surgery was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria. The severity of AKI was determined according to the SCr-based KDIGO definitions of stage AKI-1, AKI-2, and AKI-3[18]. The severe ARDS was categorized into PaO2/FiO2 ≤ 100 mmHg and cardiac failure or fluid overload were excluded corresponding to the Berlin Definition of ARDS[19]. Hypoxemia was defined as PaO2/FiO2 ≤ 300 mmHg. The Intensive Care Delirium Screening Checklist was used for the diagnosis and intervention of delirium [20]. Patients with lethargy, limb paresis-paralysis, coma, or other related symptoms received a CT examination to determine the presence of an ischemic stroke. When early postoperative paraplegia was detected, a cerebrospinal fluid drainage catheter was immediately inserted and rehabilitation training begun [21].

Statistical Analysis

Data were collected from electronic medical record retrospectively of the Data Warehouse, Department of Cardiac Surgery, Xiamen Cardiovascular Hospital of Xiamen University. Double data entry by 2 persons enables us to monitor the accuracy of the entered data. The quality and completeness of data were controlled, nd no patient were excluded due to missing or implausible values. Refer to Elettra's study[9], assuming a 25% change in serum IL-6 concentration, we need to recruit 15 patients in each arm to achieve a power of 80% with statistical significance set at 0.05. Normally distributed data were presented and mean ± standard deviation (SD), and non-normally distributed data as median (interquartile range [IQR]). Categorical data were analyzed by the chi-square test, or the Fisher's exact probability test (if necessary), and the Student's t- test was used for continuous variables. Differences between groups which were not normally distributed were analysed with a nonparametric test. All the tests were two-sided and Values of $P < 0.05$ were considered statistically significant. Poisson regression analysis was used to estimate the rate ratio (RR) of incidence of AKI and ARDS in HP group to CON group. All data analyses were performed with the R software (version 4.0.3, R Core Team2020).

Results

Patient characteristics

There were 62 patients in HP group and 59 in CON group. The mean age was 54.17 ± 11.36 years and 84.6% were male. Aortic regurgitation was common, but left ventricle dysfunction (left ventricle ejection fraction [LVEF] < 50%) was rare. One or two kidney artery involvement was 42 individuals (70%) in HP group and 44 (77.2%) in CON group without statistic difference. Preoperative characteristics and main presenting symptoms were similar between 2 groups. The data are summarized in Table 1. The mean total surgery time was about 8.5 hours, CBP time was 277.72 ± 51.14min and cardiac arrest time/selective antegrade cerebral perfusion was 45.94 ± 12.12min. Aortic root procedures and other intra-operative data were shown **in** Table 2.

Table 1
Patient demographic and preoperative characteristics

	HP group (n = 60)	CON group (n = 57)	*P-value*
Age, years	54.92 ± 11.32	53.3 ± 11.45	0.786
Male	50(83.3)	49(86)	0.69
BMI(kg/m^2)	25.45 ± 4.27	26.07 ± 4.44	0.528
Symptom onset to center, hours	8.47 ± 6.60	9.98 ± 11.44	0.200
Symptom onset to OR, hours	19.25 ± 10.51	22.37 ± 15.57	0.205
Smoking history	41 (68.3)	38 (66.7)	0.847
Alcoholdrinking history	35 (58.3)	31 (54.4)	0.44
Hypertension	34 (56.7)	29 (50.9)	0.530
Diabetes mellitus	7 (11.7)	4 (7.0)	0.39
Chronic kidney disease	1 (1.7)	1(1.8)	0.971
Chest or back pain	60 (100)	56 (98.2)	0.487
Lower-extremity ischemia	8 (13.3)	5 (8.8)	0.433
Cerebral ischemia	4 (6.7)	2 (3.5)	0.439
Aortic regurgitation	49 (81.7)	45(78.9)	0.817
Mild	27 (45.0)	27 (47.4)	
Moderate	18 (30.0)	12 (21.1)	
Severe	4(6.7)	6 (10.5)	
LVEF	64.9 ± 9.14	65.56 ± 6.7	0.119
LVEF < 50%	1(1.7)	1(1.8)	0.971
Acute cardiac tamponade	18(30.0)	9(15.8)	0.07
Baseline oxygenation index	310.79 ± 141.34	290.55 ± 114.48	0.602
Arterial hypoxemia[#]	28 (46.7)	30 (52.6)	0.519

Data are presented as number and percentage (%) or mean ± standard deviation.

HP: hemoperfusion; CON: conventional; BMI: body mass index; OR: operation room; LVEF: left ventricular ejection fraction; SCr: serum creatinine. [#]Arterial hypoxemia means the ratio of PaO2/FiO2 < 300mmHg.

	HP group (n = 60)	CON group (n = 57)	*P-value*
Admission lactate > 2.0mmol/L	21(35.0)	21(36.8)	0.84
Branch vessel involvement	3.56 ± 2.59	3.86 ± 2.17	0.510
Cerebral ischemia or infarction	4 (6.7)	2 (3.5)	0.439
Kidney artery involvement	42 (70.0)	44 (77.2)	0.409
Left or right	36 (60.0)	38, (66.7)	
Left and right	6 (10.0)	6 (10.5)	
Admission SCr > 97 μmol/L	26 (43.3)	26(45.6)	0.80
Admission SCr, (μmol/L)	114.78 ± 63.75	104.35 ± 60.19	0.797
Lower-extremity ischemia	8 (13.3)	5 (8.8)	0.560
Data are presented as number and percentage (%) or mean ± standard deviation.			
HP: hemoperfusion; CON: conventional; BMI: body mass index; OR: operation room; LVEF: left ventricular ejection fraction; SCr: serum creatinine. #Arterial hypoxemia means the ratio of PaO2/FiO2 < 300mmHg.			

Table 2
Interventions, perioperative data and lab results in 2 groups

		HP group (n = 60)	CON group (n = 57)	*P-value*
Therapeutic interventions				
Aortic root procedures				
Bentall procedure		7 (11.7)	4 (7.0)	0.389
David procedure		1 (1.7)	1 (1.8)	0.971
Aortic valve replacement		0	1 (1.8)	
Coronary artery bypass graft		3 (5.0)	4 (7.0)	0.617
Ascending aorta replacement		60 (100)	57 (100)	1.000
Total arch replacement		60 (100)	57 (100)	1.000
Elephant trunk		60 (100)	57 (100)	1.000
Perioperative data				
Total CPB time, min		279.02 ± 49.42	276.34 ± 53.34	0.543
AoCC, min		196.26 ± 44.71	197.76 ± 44.76	0.540
SACP time, min		43.47 ± 10.01	48.69 ± 13.67	0.051
Surgery time, min		507.47 ± 84.78	528.61 ± 101.22	0.239
Blood loss, ml		1517.83 ± 751.21	1471.79 ± 649.81	0.618
Blood transfusion, ml		535.83 ± 458.17	564.04 ± 387.85	0.474
PLT transfusion, units		0.95 ± 0.59	1.25 ± 0.61	0.557
Autologous blood transfusion, ml		640.83 ± 426.20	479 ± 451.52	0.921
cytokine level and lab results before and post operation				
CRP	Preoperative	29.83 ± 34.90	19.21 ± 28.21	0.736
	Immediate postoperatively	50.83 ± 47.18	91.96 ± 62.29	0.034
Lac	Preoperative	2.25 ± 1.70	2.16 ± 1.45	0.252

Data are presented as number and percentage (%) or mean ± standard deviation.

HP: hemoperfusion; CON: conventional; CPB: cardiopulmonary bypass; AoCC: aortic cross-clamp; SACP: selective antegrade cerebral perfusion; PLT, platelets. Blood transfusion: the amount of packed red blood cells and frozen plasma transfusion. IL-6, interleukin-6(pg/ml); CRP, C-reactive protein(mg/L); Lac: lactate (umol/L);PLT, platelets(*10^9/L); MYO, myoglobin(ng/ml).

		HP group (n = 60)	CON group (n = 57)	*P-value*
	Immediate postoperatively	4 ± 2.43	5.39 ± 3.56	0.005
	Clearance to normal, hours	7 (3–24)	20(10–33)	0.053
PLT	Preoperative	186.27 ± 62.03	173.29 ± 62.72	0.817
	Lowest value postoperative D1	110.83 ± 36.55	128.54 ± 46.70	0.264
MYO	Preoperative	184.69 ± 537.68	169.39 ± 401.18	0.931
	Immediate postoperatively	982.14 ± 707.213	1351.50 ± 1521.91	0.031
Data are presented as number and percentage (%) or mean ± standard deviation.				
HP: hemoperfusion; CON: conventional; CPB: cardiopulmonary bypass; AoCC: aortic cross-clamp; SACP: selective antegrade cerebral perfusion; PLT, platelets. Blood transfusion: the amount of packed red blood cells and frozen plasma transfusion. IL-6, interleukin-6(pg/ml); CRP, C-reactive protein(mg/L); Lac: lactate (umol/L);PLT, platelets(*10^9/L); MYO, myoglobin(ng/ml).				

Primary outcomes

The serum IL-6 level was not significantly different between 2 groups (21.21pg/ml in HP group vs. 22.11pg/ml in CON group, *P = 0.921*) before surgery, but the values were increased rapidly postoperatively, about 7–9 times, and were lower in HP group than in CON group (146.13pg/ml vs. 205.73pg/ml, *P = 0.020*). On postoperative day 1 and day 2, IL-6 levels had the similar trends. Details were shown in Fig. 2.

Key second outcomes

The HP group had a significantly lower incidence of AKI compared to CON group (15/59, 25.4% vs. 25/56, 44.64%, *P = 0.001*) and 2 patients with chronic kidney disease excluded from the analysis. The rates of AKI stage 2 or 3 per KDIGO classification were 10.2% (6/59) in HP group compared 21.4% (12/56) in CON group *(p = 0.097)*. The overall incidence of hypoxemia was close to 100%, however, the severe ARDS in HP group was 18.3% (11/60) compared to 35.1% (20/57) in conventional group (*P = 0.04)*. The main outcome analysis showed that the RR of incidence of AKI was 0.57 (95% CI 0.35–0.79, *p = 0.012*) in HP group compared to conventional group, and the RR of incidence of severe ARDS was 0.52 (95% CI 0.28–0.92, *p = 0.043*). But the dependence on renal replacement therapy and duration of mechanical ventilation similar. Primary outcome data are summarized in Table 3.

Table 3
Postoperative outcomes and data in 2 groups

	HP group (n = 60)	CON group (n = 57)	*P-value*
Blood loss in first 24 hours, ml	754.38 ± 381.67	770.33 ± 666.72	0.876
Re-exploration for bleeding	0 (0)	1(1.8)	
AKI *	15 (25.4)	25 (44.6)	0.001
AKI stage 1	9 (15.3)	13 (23.2)	
AKI stage 2	5 (8.5)	10 (17.9)	
AKI stage 3	1 (1.7)	2 (3.6)	
RRT*	4 (6.8)	6 (10.7)	0.46
Arterial hypoxemia	58 (96.7)	57 (100)	
Severe ARDS	11 (18.3)	20 (35.1)	0.04
Ventilator support time, days	4.43 ± 4.28	4.47 ± 4.08	0.324
Ventilator support > 7 days	11(18.3)	9 (16.7)	
Reintubation	4 (6.7)	5 (8.8)	
Tracheotomy	3(5.0)	4(7.0)	
Paraplegia	4 (6.7)	2 (3.5)	0.44
Stroke	3 (5.0)	2 (3.5)	0.69
Delirium	19 (31.7)	19 (33.3)	0.84
Seizure	4 (6.7)	3 (5.3)	
Secondary intervention of the distal aorta with endovascular stent	2(3.3)	4(7.0)	0.43
LOS-ICU	7.88 ± 4.08	7.86 ± 5.69	0.373
ICU stay > 10 days	10 (16.7)	13 (22.8)	0.488
LOS-hospital, days	20.33 ± 7.91	20.84 ± 8.25	0.413

Data are presented as mean ± standard deviation, or number and percentage.

HP: hemoperfusion; CON: conventional; OR: operation room; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; RRT: renal replacement therapy; LOS: length of stay; ICU: intensive care unit.*Two patients with chronic kidney disease were excluded from the analysis, and therefore 59 patients in HP group and 56 patients in CON group included in AKI analysis.

	HP group (n = 60)	CON group (n = 57)	*P-value*
Hospital stay > 28 days	6 (10.0)	10 (17.5)	0.287
In-hospital death	2	2	
Data are presented as mean ± standard deviation, or number and percentage.			
HP: hemoperfusion; CON: conventional; OR: operation room; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; RRT: renal replacement therapy; LOS: length of stay; ICU: intensive care unit.*Two patients with chronic kidney disease were excluded from the analysis, and therefore 59 patients in HP group and 56 patients in CON group included in AKI analysis.			

Additional secondary outcomes

The postoperative mortality was 4/121, 3.31%, for 2 patients in each group were died within the first postoperative week and without extra hospital deaths. The incidence of bleeding, delirium, stroke and other postoperative complications were similar between the groups. There was no difference in length of ICU and hospital stay, but the patients of ICU stay > 10 days was less in HP group than in CON group with no statistical significant (10/60, 16.7% vs. 13/57, 22.8%, *P = 0.488*) and hospital stay > 28 days had the same trend. Blood loss and transfusion and secondary outcome data are summarized in Table 3.

Change trends in C-reactive protein (CRP) were similar with IL-6. The peak postoperative serum lactate level and the lactate clearance time were lower in HP group. MYO had slight increase before surgery and then increased rapidly to several times postoperatively. The value of MYO was also lower in HP group. Platelets were decreased postoperatively but with no statistical difference in 2 groups. Details were shown in Table 2.

Comparison of IL-6 levels with major complications

Postoperative IL-6 levels were positively correlated with the incidence of AKI in the 115 patients. With respect to AKI, the mean IL-6 immediately postoperative was higher in patients with AKI compared to patients without AKI (232.18 ± 197.89 pg/m vs147.36 ± 71.15pg/ml, *P = 0.003*). On postoperative day 1, IL-6 decreased rapidly. Severe ARDS followed the same trend with AKI but no statistical difference. Results are summarized in Fig. 3.

Discussion

The study is the first to focus on the protective effect of hemoperfusion therapy on ATAAD surgery with characteristics of severe inflammatory response and poor prognosis. Our results revealed that adding a HA-380 cartridge to conventional CPB circuit could not only reduce the high levels of IL-6 and CRP but also decrease the accidence of AKI and severe ARDS postoperatively. While the length of postoperative ICU stay was similar between the groups, patients in HP group seemed to require less treatment intensity.

Adding hemoperfusion in CPB was well tolerated and safe, with no device related adverse events occurring.

ATAAD is a life-threatening medical emergency with high morbidity and mortality rates [22]. The most efficient way to save fatal consequences is emergent operation and most of the survival benefits come from advances in surgery recently [14]. Ascending and total arch replacement along with aortic-valve replacement or repair, combined with stent elephant trunk implantation into the true lumen of the distal aorta (Sun's operation) is an accepted surgical management of ATAAD, and has resulted in a decrease of the in-hospital mortality to 4.7%[17, 22]. The study reported the surgical mortality was 3.31%. Both ATAAD itself and surgical procedure are non-infectious stimuli for systemic inflammation and that is characterized by elevated plasma concentrations of complement, secretion of pro-inflammatory cytokines and ultimately tissue and multisystem organ destruction [23, 24]. Characterized by prolonged CPB time, lower body temperature and larger amount of blood loss, an ATAAD surgery has more severe inflammatory response [25]. IL-6 exhibits expression in all major cell types which is an important member of the cytokine family, and regulates hematopoiesis, immune homeostasis, and various metabolic processes [26]. The level of IL-6 elevated on admission, increased several times postoperative immediately and decreased in the following days indicating that both dissection itself and surgery stimulates inflammatory responses and the latter being more serious in this study. The single peak of serum IL-6 indicated that cytokine adsorption could attenuate the inflammatory response during ATAAD surgery.

Extracorporeal cytokine adsorption, known as hemoadsorption, using materials with high adsorptive capacity applied to a number of disorders [1].The HA-380 cartridge is a novel hemoadsorption device that contains neutral macroporous beads, and is capable of removing 10 to 60 kDa molecules from blood including various cytokines [3]. IL-6 has been identified as a diagnostic tool, and frequently as a potential clinical target of hemoperfusion treatment [27]. Another inflammation biomarker CRP, an acute-phase protein regulated by pro-inflammatory cytokines, were higher in aortic dissection and independently associated with worse short-term mortality and poor prognosis[28, 29]. Although the clinical benefts was uncertain in sepsis, a Chinese study showed that applying hemoperfusion therapy during CPB had significantly lower levels of IL-6, IL-8, and IL-10 and improve recovery after cardiac surgery[5]. In this study, the lower IL-6 and CRP level postoperatively were found in HP group compared to conventional group. And so a benefits of relevant clinical outcomes as AKI and severe ARDS were found in HP group. But another study showed hemoperfusion was not associated with inflammatory cytokines decrease nor with outcome improvement [9]. Different from ATAAD surgery, the study populations had a shorter CPB time and no requirement of deep hypothermic circulatory arrest might be associated with low inflammatory response.

Applying hemoperfusion therapy can both clear inflammatory cytokines and benefit in kidney function in this study. The pathophysiology of cardiac surgery associated AKI is very complex, one is hemolysis from the prolonged duration of CPB[30–32].The incidence of AKI (40/115, 34.8%) was higher than selected cardiac surgery without aortic arch repair[25]. There was also no difference in branch vessel and renal

artery involvement between 2 groups for renal artery dissection is an important risk factor for AKI. Obviously, HP group had a lower incidence of AKI. The HA-380 cartridge can partly adsorb myoglobin (18 kDa) and plasma-free hemoglobin (60 kDa)[3, 33, 34] just as lower myoglobin level in HP group. A greater increase of plasma-free hemoglobin during cardiac surgery was observed and associated with higher incidence of AKI, and the use of a CytoSorb hemoperfusion cartridge could significant reduce hemoglobin at the end of CPB [11, 35]. Thus, the renal protective effects of hemoperfusion include not only by inflammatory cytokines removal but also by free haemoglobin and myoglobin clearance[3].

A systemic inflammatory state induced by ATAAD and surgery is also associated with ARDS[36, 37]. The incidence of severe ARDS was 26.5% (31/117) in our study that the incidence was higher but the mortality was lower than previous report[36, 37]. HA-380 cartridge resulted in a lower incidence of ARDS and the lung-protective effect of hemoperfusion had been reported before[38]. There was no impact on ventilator support time, or the incidence of re-intubation, and also no difference in delirium, stroke, paraplegia, and other postoperative outcomes. The reason might be that ATAAD is a catastrophic condition and surgical repair is a complex operation. The postoperative support and overall outcomes are influenced by associated complications such as malperfusion syndrome, mesenteric ischemia, cerebral infarction, and low cardiac output syndrome [17] which cannot be rescued by hemoperfusion therapy.

An in vitro study of the biocompatibility and cytotoxicity of Jafron cartridge showed there was no increase of monocytes, necrosis, or apoptosis and cytotoxicities[3]. No extra anticoagulation required for heparinization during CPB period. Our results also showed no significant blood loss and more platelets transfusion in HP groups.

One strength of the study is that the first report to evaluate effective of hemoperfusion therapy during emergent surgery of an ATAAD. We strictly selected patients with symptom onset to operating room less than 72 hours and receiving total arch replacement based on the understanding that this emergency situation and arch operation had more severe inflammatory response and worse prognosis. Single peak inflammatory response of surgery and no extra anticoagulation requirement were the other consideration. This work indicates the potential for enhancing the hemoperfusion therapy in complex cardiac surgery.

The study is not without limitations, most of which is the retrospective study. Our study depended on clinical data with potential confounders for patients were not randomized and the interventions were compared to that of a historical cohort group. From September 2021 to February 2022, the second half of the study period, adding HA-380 cartridge in CPB was the unique variable of ATAAD management comparing to previous 6 months. All patients at the study period who did meet the eligibility criteria were totally enrolled in the analysis in order to avoid selection bias and provide comparable data. Another limitation is a single center study. Reported survival rates for ATAAD surgery vary widely among different centers[39]. Both high volume center, standardized protocol and experienced surgeons confirmed a net positive impact on ATAAD outcomes. The Xiamen Cardiovascular Hospital is the center of 4-hours life-saving circle and chest pain center of Southeast China, nearly 200 ATAAD patients per year were hospitalized. Although we have routine surgical produce and medical treatment with unified mode in our

hospital with the surgery mortality less than 5%, it is obvious that multiple homogeneous centers must show superior performance than single center study. The third is that methylprednisolone was prophylactically administered to patients, and it can greatly decrease the level of the inflammatory response. There are still inconclusive in routine use of steroids in ATAAD operation although steroids might be harm in other CPB operation [40, 41]. Additionally, although the HP group had lower inflammatory mediators and better clinical outcomes, does not determine they have a causation relationship. Finally, cytokine levels and lab results such as plasma-free hemoglobin, IL-1, IL-10, TNF, and macrophage migration inhibitory factor did not measure. Nevertheless, adding hemoperfusion therapy in CPB circuit offers an easy and safe method to improve organ functions post ATAAD surgery.

Conclusion

The emergent ATAAD surgery had a higher cytokine concentrations than dissection itself. The HA-380 cartridge combined to CPB circuit could effectively attenuate the postoperative level of IL-6, CRP, myoglobin and lactate, and reduced the incidence of AKI and severe ARDS.

Abbreviations

AKI: acute kidney injury; AMI: acute myocardial infarction; ARDS: acute respiratory distress syndrome; ATAAD: Acute type A aortic dissection; CPB: cardiopulmonary bypass; CRP: C-reactive protein; HP: hemoperfusion; ICU: intensive care unit; interleukin-6 (IL-6); KDIGO: Kidney Disease Improving Global Outcomes; LVEF: left ventricle ejection fraction; PLT: platelet; RR: rate ratio.

Declarations

Ethics approval and consent to participate

The study was followed in accordance with the ethics committee of the Xiamen Cardiovascular Hospital of Xiamen University and with the Helsinki Declaration of 1975 (Study title: The study of adding a resin hemoperfusion therapy in CPB during central repair of acute type A aortic dissection, ethics approval number: XXY-AF/EC-09.01/2.0).Written informed consent to participate in the study and consent to publish was obtained from each patient.

Consent for publication

Not applicable

Availability of data and materials

The dataset analysed during the current study is available from the corresponding author on reasonable request.

Competing interests

All authors declared that they have no competing interests.

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Authors' contributions

The corresponding author (XJW) was in charge of study design. The first author (JXW, BC) was responsible for manuscript writing and cooperated with the rest five authors (JHX, HLC, LHL, WQZ and LL) in clinical research work. JXW was in charge of data collection and experiment, BC was responsible for data analysis. HLC, LHL, WQZ and LL were responsible for sample collection, experiment technical and material support during the study. All authors have read and approved the publication of this manuscript.

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Figures

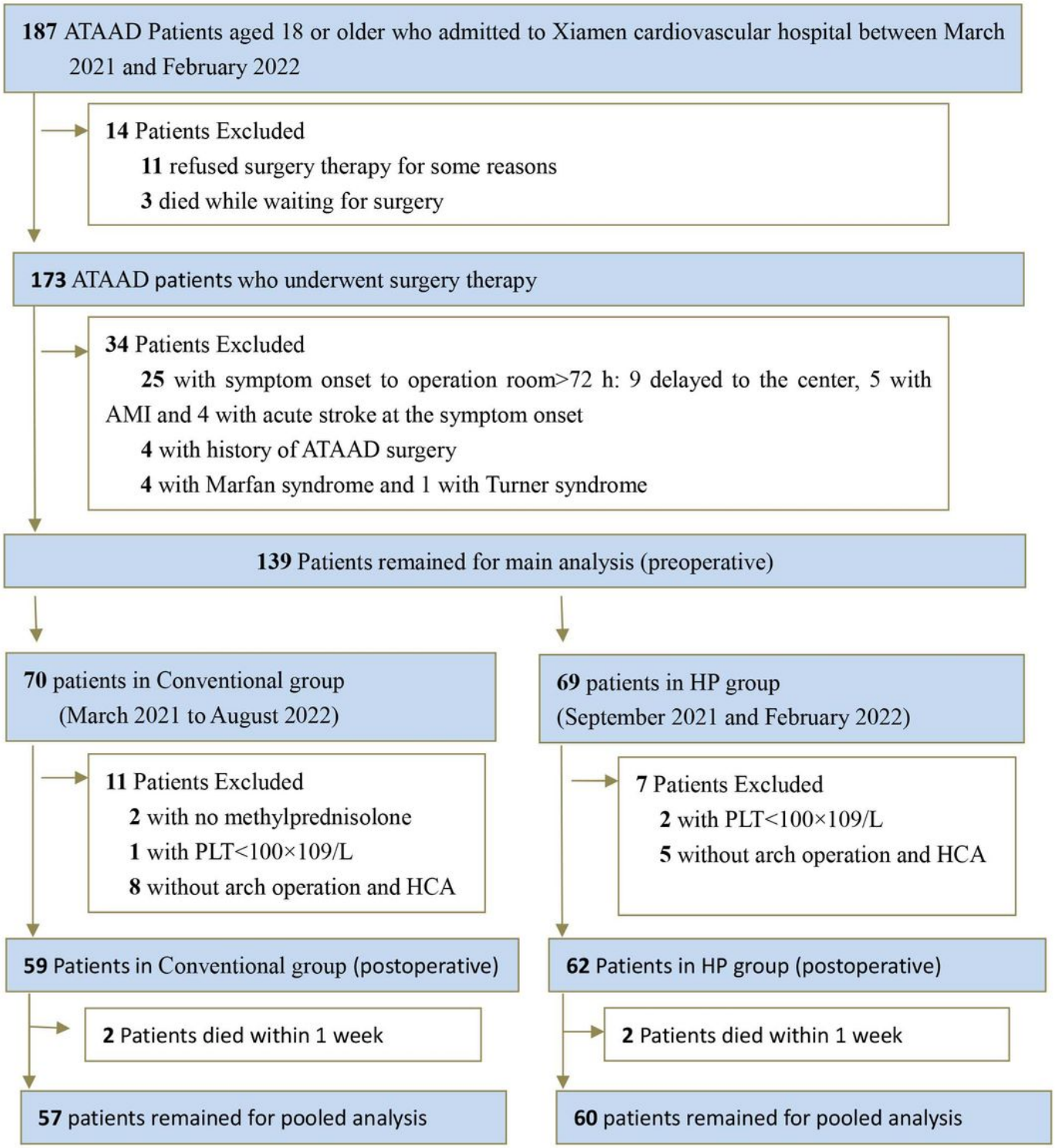
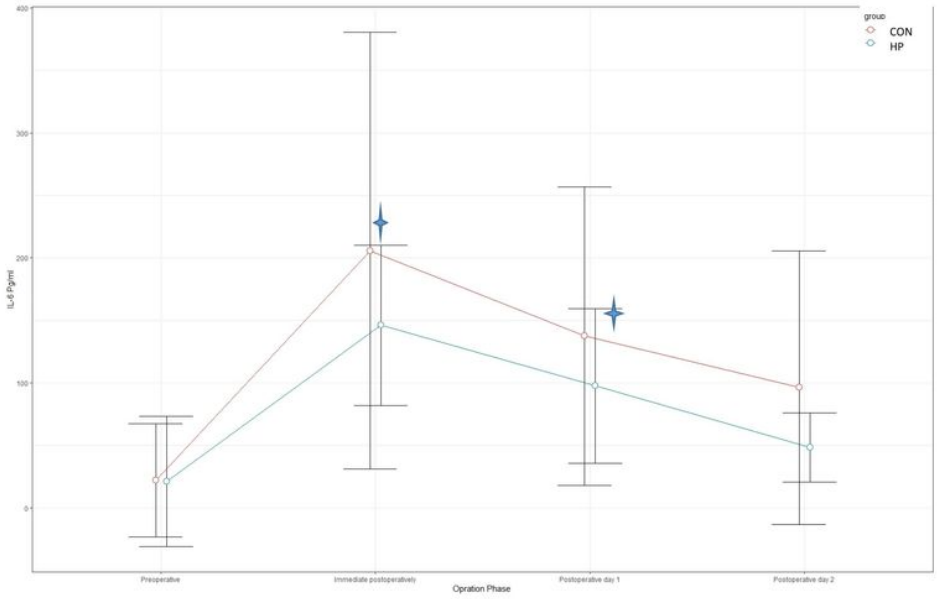


Figure 1

Flow diagram of patient inclusion.

ATAAD: acute type A aortic dissection; CR: central repair operation; AMI: acute myocardial infarction; CON: conventional; HP: hemoperfusion; PLT: platelet; HCA: hypothermic circulatory arrest.

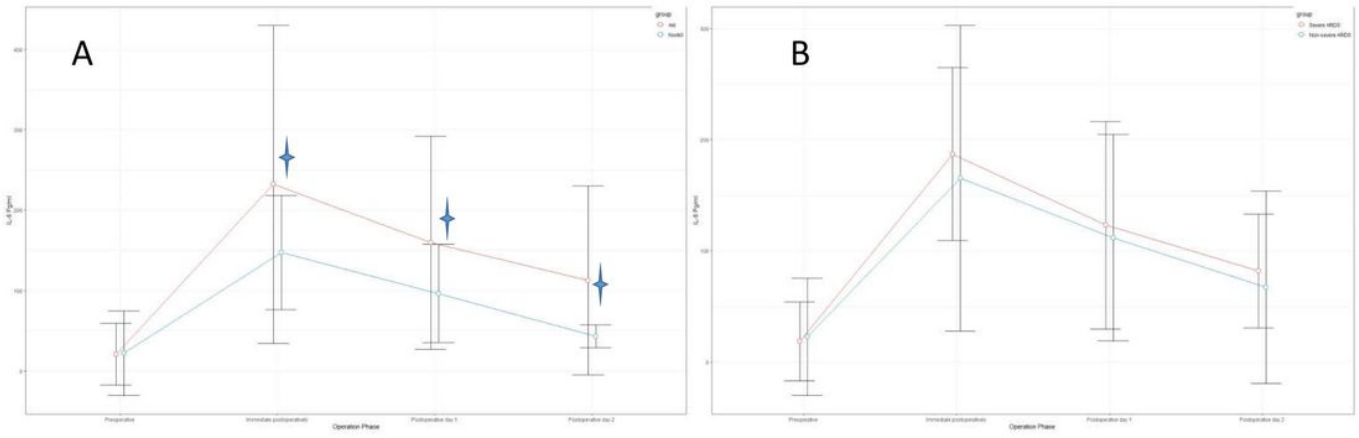


	HP group(n=60)	CON group(n=57)	*P value*
Preoperative	21.21±51.95	22.11±45.22	0.921
Immediate postoperatively	146.13±64.15	205.73±174.72	0.020
Postoperative day 1	97.63±61.95	137.54±119.39	0.031
Postoperative day 2	48.48±27.71	96.25±109.40	0.127

Figure 2

Comparison of IL-6 levels of the HP group and CON group.

IL-6 levels across time postoperatively were lower in HP group compared with the CON group. HP: hemoperfusion; CON: Conventional; IL-6, interleukin-6.



	AKI(n=40)	No AKI(n=75)	*P value*	Severe ARDS(n=30)	Non-severe ARDS(n=87)	*P value*
Preoperative	20.70±38.49	22.11±52.68	0.888	18.70±35.45	22.71±52.66	0.696
Immediately postoperative	232.18±197.89	147.36±71.15	0.003	186.97±77.68	165.36±137.30	0.466
Postoperative day 1	159.47±132.51	96.27±61.37	0.001	123.02±93.26	111.71±92.77	0.594
Postoperative day 2	112.69±117.57	43.30±14.39	0.032	81.76±51.20	67.16±86.54	0.700

Figure 3

Comparison of IL-6 levels in patients with and without AKI& severe ARDS.

IL-6, interleukin-6; AKI: acute kidney injury. ARDS: acute respiratory distress syndrome. **A: with and without AKI** Postoperatively, IL-6 levels were significantly higher in patients with AKI compared to those without AKI. *Two patients with chronic kidney disease were excluded from the analysis. **B: with and without severe ARDS** Postoperatively, patients with severe ARDS had higher IL-6 levels compared to patients without ARDS, but differences were not statistically significant.