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Mannitol Is Associated with Less Postoperative Delirium after Aortic Valve Surgery in Patients Treated with Bretschneider Cardioplegia

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Abstract

Background Heart surgery with extracorporeal circulation (ECC) often leads to postoperative delirium (POD). This is associated with increased morbidity resulting in longer hospital stay and associated costs. The purpose of our study was to analyze the effect of intraoperative mannitol application on POD in patients undergoing elective aortic valve replacement (AVR).

Materials and Methods In our retrospective single-center study, 259 patients underwent elective AVR, using Bretschneider cardioplegic solution for cardiac arrest, between 2014 and 2017. Patients were divided in mannitol ($n = 188$) and nonmannitol ($n = 71$) groups. POD was assessed using the confusion assessment method for the intensive care unit (ICU). Statistical significance was assumed at $p < 0.05$.

Results Baseline patient characteristics did not differ between the groups. Incidence of POD was significantly higher in the nonmannitol group (33.8 vs. 13.8%; $p = 0.001$). These patients required longer ventilation time (24.1 vs. 17.1 hours; $p = 0.021$), higher reintubation rate (11.3 vs. 2.7%; $p = 0.009$), ICU readmission (12.7 vs. 4.8%; $p = 0.026$), prolonged ICU (112 vs. 70 hours; $p = 0.040$), and hospital stay (17.8 vs. 12.6 days; $p < 0.001$), leading to higher expenses (19,349 € vs. 16,606 €, $p < 0.001$). A 30-day mortality was not affected, but nonmannitol group showed higher Simplified Acute Physiology Score II score (32.2 vs. 28.7; $p < 0.001$). Mannitol substitution was independently associated with lower incidence of POD (odds ratio: 0.40; 95% confidence interval: 0.18–0.89; $p = 0.02$).

Conclusion Treatment with mannitol during ECC was associated with decreased incidence of POD. This was accompanied by shorter ventilation time, ICU and hospital stay, and lower treatment expenses.

Keywords
- aortic valve
- postoperative care
- intensive care
- outcomes

Introduction

Postoperative delirium (POD) is a common neurological complication after surgery, most often seen in elderly patients. Besides age, cardiac function, diabetes, vascular disease, and pre-existent cognitive impairment, POD is also independently associated with invasiveness and duration of cardiac surgery.[1] In this regard, patients undergoing cardiopulmonary bypass (CPB) seem to be vulnerable for the development of POD, which is diagnosed in ≈30 to 52% in this population.[2,3] Most notably, POD is associated with longer intensive care unit (ICU) and hospital stay, long-term cognitive impairment, and

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increased mortality,[4–6] consequently leading to increase in treatment expenses.[7,8] Therefore, attempts to reduce POD in these patients are important.

It has been reported that CPB itself can promote the development of POD.[9] Preparation of the CPB is not uniform: hypo-oncotic priming solutions of the heart–lung machine (HLM) can result in interstitial fluid retention and lead to cerebral edema; the latter has been shown to promote encephalopathy and delirium, but the underlying mechanism remains unclear.[10] In contrast, an increased oncotic pressure is beneficial for maintaining a sufficient mean arterial pressure (MAP) and has been shown to improve organ perfusion.[11] As a consequence, colloids such as human albumin (HA) or hydroxyethyl starch (HES) are often added to the priming solution of the HLM.[12,13] However, a clear advantage for using colloidal solutions could not be demonstrated.[12,14] Moreover, studies report that the use of HES and HA are associated with renal failure,[15,16] even though conflicting data exist with respect to nephroprotective properties of HA, showing reduced risk of acute renal failure after off-pump coronary artery bypass surgery.[17] Most importantly, HES administration was related to early POD development.[18]

Mannitol is commonly used to reduce intracranial pressure and edema due to its osmodiuretic effects[19] and may be added to the priming solution during CPB to maintain higher oncotic pressure.[20] But so far, no study has examined an association between mannitol application during CPB and POD. Therefore, this study aimed to examine the effect of mannitol supplementation during CPB on the development of POD and other parameters of postoperative outcome in a homogenous cohort of patients undergoing elective surgical aortic valve replacement (AVR).

Materials and Methods

Patient Selection and Group Definition

This retrospective single-center study was performed on 259 patients, who were admitted for first time elective surgical AVR between 2014 and 2017. Indications for AVR were aortic stenosis, aortic regurgitation, or elective AVR. All patients undergoing concomitant heart surgeries (e.g., coronary artery bypass graft surgery, other valve procedures, etc.) or David/Bentall procedures were excluded from the study. One patient was diagnosed with aortic valve endocarditis, but this was not associated with enhanced inflammatory parameters and only diagnosed in echocardiography. In all patients included in our study, retrograde autologous priming (RAP) of the HLM was performed. All patients receiving albumin or crystalloid priming were excluded from this study. A comprehensive dataset of pre-, intra-, and postoperative parameters was generated by review of patient charts and IT-based datasets. Information on preoperative baseline characteristic, risk factors, and comorbidities, such as renal (need for hemodialysis) or liver failure, were recorded. Also, we screened all available preoperative patient's data (recent medical reports, information provided by the patients and/or family members) with respect to cerebrovascular insults, neurological and cognitive impairment (e.g., preexisting dementia, Alzheimer's and Parkinson's disease, epilepsy), psychiatric or mental disorders (e.g., schizophrenia, depression), daily medication, and drug or alcohol abuse.

Within the aforementioned period of time, all patients, except those with complicated preoperative course, for example, organ failure, preoperative catecholamine therapy, the need for mechanical circulatory support (MCS), or the above-described psychic or mental disorders and drug or alcohol abuse, were included in this study. The preoperative risk score European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was calculated for each patient. All patients who were eligible for this retrospective study were divided into two groups: 188 patients having received mannitol during CPB (mannitol group) and 71 patients having not received (nonmannitol group).

Surgical Procedure and Mannitol Administration

All patients were classified as American Society of Anesthesiologists III and IV, and a standard anesthetic protocol was performed using sufentanil, etomidate, and rocuronium for induction of anesthesia followed by endotracheal intubation. Anesthesia was maintained using sufentanil and sevoflurane. Standard monitoring comprised peripheral oxygen saturation, electrocardiogram, temperature, and invasive arterial blood pressure. Furthermore, a trilumen central venous catheter, a high-flow sheath introducer, as well as a urinary catheter was placed. During CPB, sevoflurane was administered continuously during CPB. Surgical procedure was similar in all patients: complete median or superior median ministernotomy was performed. To achieve an activating clotting time of $>$450 seconds, anticoagulation with 400 to 500 U/kg sodium heparin was initiated. After cannulation of the ascending aorta and the right atrium, CPB was established using a Terumo Advanced Perfusion System 1 (Terumo Cardiovascular Systems, Ann Arbor, Michigan, United States). The extracorporeal circuit included a venous hardshell cardiotomy reservoir (Maquet, Wayne, New Jersey, United States), a roller pump system, and a membrane oxygenator (Quadrox oxygenator, Maquet) equipped with a heat exchanger and an arterial filter system. The nonheparin-coated tube system was primed with crystalloid solution ($\approx$1,000 mL Jonosteril, Fresenius, Bad Homburg, Germany) and 10,000 U of heparin. In all patients, RAP was performed after connecting the HLM to the introduced cannulas.

In this study, 188 patients were treated with 0.5 g/kg body weight mannitol solution (Osmosteril 20%, Fresenius-Kabi GmbH, Bad Homburg, Germany) during extracorporeal circulation (ECC) according to intraoperative diuresis and fluid intake: If intraoperative diuresis was less than 50 mL/h after aortic unclamping and/or more than 3,000 mL crystalloid solution were infused during ECC, mannitol was administered as bolus into the HLM to augment diuresis and to minimize fluid movement to the extravascular space. All other patients did not receive mannitol. The mannitol dosage was in accordance with other studies.[21,22] Mannitol was not part of the priming solution, as no effects of mannitol on osmolarity of the priming solution have been observed in patients with normal cardiac and renal function.[21] Cardioprotection and myocardial arrest were achieved using Bretschneider HTK-cardioplegia (Custadiol, Dr. Franz Kohler

Chemie GmbH, Bensheim, Germany). A nonpulsatile pump flow of 2.2 to 2.6 L/min/m^2 was conducted to maintain a MAP of 50 to 60 mm Hg during CPB.

Postoperative Care

After the surgical procedure, all patients were transferred to the ICU, where sedation was achieved using propofol and sufentanil. Airway pressure release ventilation was performed, with an inspiratory:expiratory ratio of ≈1.5:2 seconds, corresponding to a respiratory rate of ≈17 breaths/min. Tidal volume of 6 to 8 mL/kg was used, and positive inspiratory pressure was set to 20 cm H_2O, while positive end-expiratory pressure of 10 cm H_2O was applied. The fraction of insufflated oxygen was adjusted according to arterial blood gas analysis. Early extubation and transfer to the intermediate care ward were attempted in all cases. Further analgesic regimen followed piritramide bolus injection (3–5 mg intravenous).

Duration of surgery, CPB and aortic cross-clamping time, parameters of organ function, and other routine laboratory variables were recorded. Outcome data further included: ventilator-associated pneumonia, need for reintubation, renal failure with need for continuous venovenous hemofiltration or -dialysis (CVVH/HD, length of ICU and hospital stay, nurse workload score ("Therapeutic Intervention Scoring System" [TISS]-10), and monitoring of the "Simplified Acute Physiology Score II" (SAPS II), as well as 30-day mortality and the total hospital treatment costs.

Assessment of Postoperative Delirium

For assessment of POD, criteria of the Diagnostic and Statistical Manual of Mental Disease, Fifth Edition were applied.[23] Delirium is characterized by fluctuating clinical course, for example, memory deficit, disorientation, language, visuospatial ability, or perception disorders. The development of delirium within short time was assessed daily during ICU stay using the confusion assessment method for the intensive care unit (CAM-ICU) flowsheet.[24] Patients with sedation ("Richmond Agitation and Sedation Scale" score < -3), stroke symptoms, or nonnative German speakers were excluded from the study. Patients with a positive CAM-ICU test were defined as POD positive.

Statistical Analysis

Data are presented as means with standard deviation. Continuous variables were tested using either the Student's *t*-test, or, in the case of a nonnormal distribution (D'Agostino's K-squared test), the Mann–Whitney's *U* test, if two groups were compared at one time point. Linear mixed models were used to investigate differences between mannitol and nonmannitol groups on the time course of various parameters of interest measures (lactate, serum creatinine, and bilirubin). Categorical data were expressed as percentages and tested using the Pearson's chi-square test. A *p*-value of <0.05 was considered statistically significant.

Univariable and multivariable logistic regression were employed to investigate risk factors for POD. The following risk factors were investigated: Patients age, diabetes mellitus, white blood cell (WBC) at admission, preoperative sodium, creatinine, hemoglobin and hematocrit values, EuroScore II, aortic cross-clamping time, CPB time, reperfusion time, minimum and mean sodium concentrations during CPB, minimum intraoperative hemoglobin, minimum intraoperative arterial oxygen saturation, minimum intraoperative MAP, mannitol substitution during CPB, amount of cardioplegic solution, fluid balance after CPB, amount of blood products transfusion during surgery, total diuresis during CPB, perioperative ventilation time, need for postoperative reintubation, need for postoperative CVVH/HD or dialysis, pneumonia, SAPS II score 24 hours after ICU admission, postoperative maximum creatinine, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and MAP 1 hour after surgery.

IBM SPSS statistics (SPSS Inc., Chicago, Illinois, United States, version 25) and R (version 3.6.2, R Core Team [2018]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) were used for statistical analysis.

Results

No significant differences in terms of demographic and preoperative baseline characteristics were observed between the two groups: Most importantly, no differences were seen in pre- and postoperative serum creatinine, bilirubin, and ALT/AST levels (►**Table 1** and ►**Supplementary Table S1** [online only]), indicating no differences in renal and liver function in both groups. The pre- and postoperative lactate levels as parameter for an anaerobic metabolism and thus surrogate parameter of reduced organ perfusion did not show any significant difference between the groups. Also, the hemoglobin concentration, WBC, and platelet count before and after surgery were not different (►**Table 1** and ►**Supplementary Table S1** [online only]).

►**Table 2** summarizes intraoperative data, sowing no differences with respect to duration of surgery, aortic cross-clamping time and CPB time, MAP, and amount of cardioplegic solution. Fluid balance during CPB was significantly less positive in mannitol compared with the nonmannitol patients, being associated with higher diuresis and filtered fluid amount in the same group. No difference was observed with respect to intraoperatively transfused red blood cell concentrates. Beside hemoglobin and lactate concentration, minimum and mean serum sodium concentrations during CPB were similar in both groups, going along with comparable postoperative diuresis and total fluid balance after 24 hours (►**Supplementary Table S1** [online only]).

Further, data on postoperative outcome and adverse events are displayed in ►**Table 3** and ►**Supplementary Table S1** (online only): no difference was seen with respect to use of MCS, need for cardiopulmonary resuscitation, incidence of pneumonia, number of postoperative myocardial infarction, atrioventricular block higher than second degree, need for pacemaker implantation, CVVH/D, and rethoracotomy. However, most importantly, the incidence of POD was significantly higher in the nonmannitol compared with the mannitol group. Furthermore, absence of mannitol was associated with longer

Table 1 Preoperative patients' characteristics

	Total ($n = 259$)	Mannitol ($n = 188$)	Nonmannitol ($n = 71$)	*p*-Value
Age (y)	66.6 ± 10.2	66.0 ± 10.8	67.9 ± 8.1	0.182
Female	88 (34.0%)	64 (34.0%)	24 (33.8%)	0.971
Height (m)	1.74 ± 0.3	1.72 ± 0.1	1.80 ± 0.7	0.126
Weight (kg)	82.7 ± 15.2	82.4 ± 15.1	83.5 ± 15.5	0.603
BMI (kg/m^2)	28.2 ± 9.2	27.8 ± 4.8	29.3 ± 15.8	0.248
EuroSCORE II	1.83 ± 0.75	1.80 ± 0.69	1.92 ± 0.90	0.207
Diabetes mellitus	56/253 (22.1%)	39/183 (21.3%)	17 (24.3%)	0.610
Hemoglobin (g/dL)	13.4 ± 1.9	13.5 ± 1.8	13.3 ± 1.9	0.502
WBC (g/L)	7.6 ± 2.5	7.7 ± 2.5	7.4 ± 2.5	0.490
Creatinine (mg/dL)	1.1 ± 0.6	1.0 ± 0.4	1.1 ± 0.9	0.341
Bilirubin (mg/dL)	0.7 ± 0.6	0.7 ± 0.7	0.6 ± 0.4	0.435
ALT (U/L)	31.0 ± 15.6	31.5 ± 15.1	29.1 ± 17.1	0.455
AST (U/L)	26.7 ± 17.3	27.1 ± 18.9	25.3 ± 11.2	0.508
Left ventricular ejection fraction				
> 50%	218 (84.1%)	154 (81.9%)	64 (90.1%)	0.296
30–50%	35 (13.5%)	29 (15.4%)	6 (8.5%)	
< 30%	6 (2.3%)	5 (2.7%)	1 (1.4%)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; Mannitol, patients received mannitol during extracorporeal circulation; Nonmannitol, patients without mannitol treatment; WBC, white blood cell.
Notes: Summary of preoperative patients' characteristics. Values are expressed as mean ± standard deviation, or as number and percentage (in bracket). Significant changes are displayed in italics.

Table 2 Intraoperative data

	Total ($n = 259$)	Mannitol ($n = 188$)	Nonmannitol ($n = 71$)	*p*-Value
Time to skin closure (min)	230.6 ± 58.7	232.0 ± 59.2	226.8 ± 57.7	0.284
CPB time (min)	120.8 ± 111.4	115.0 ± 29.4	112.5 ± 24.5	0.695
Aortic clamp time (min)	86.8 ± 41.0	85.2 ± 21.3	82.7 ± 18.8	0.607
Cardioplegic solution (mL)	1,776.8 ± 354.9	1,792.2 ± 384.6	1,735.9 ± 258.3	0.671
Fluid balance on CPB (mL)	223.5 ± 1,240.5	132.5 ± 21.3	464.6 ± 922.7	*0.006*
Filtered fluid volume (mL)	2,126.7 ± 1,282.4	2,165.3 ± 1,161.3	2,024.6 ± 1,563.5	*0.046*
Diuresis during CPB (mL)	369.8 ± 339.0	386.3 ± 326.0	326.3 ± 370.1	*0.022*
MAP				
Minimum (mm Hg)	54.6 ± 8.6	54.4 ± 9.0	55.1 ± 7.6	0.578
Maximum (mm Hg)	67.0 ± 9.1	66.6 ± 9.3	68.0 ± 8.3	0.098
Hemoglobin concentration				
Minimum (g/dL)	9.58 ± 1.61	9.54 ± 1.63	9.70 ± 1.55	0.523
Maximum (g/dL)	11.11 ± 1.40	11.14 ± 1.43	11.05 ± 1.30	0.981
Serum sodium during CPB				
Mean (mmol/L)	132.40 ± 3.90	132.29 ± 3.83	128.18 ± 6.07	0.480
Minimum (mmol/L)	128.54 ± 5.86	132.69 ± 4.09	129.51 ± 5.19	0.080
RCC (units)	0.35 ± 0.77	0.32 ± 0.71	0.42 ± 0.90	0.625
Maximum lactate (mmol/L)	1.53 ± 1.89	1.60 ± 2.20	1.35 ± 0.51	0.444

Abbreviations: CPB, cardiopulmonary bypass; MAP, mean arterial pressure; Mannitol, patients received mannitol during extracorporeal circulation, Nonmannitol, patients without mannitol treatment; RCC, red blood cell concentrate.
Notes: Summary of surgery-related intraoperative variables. Values are expressed as mean ± standard deviation. Significant changes are displayed in italics.

Table 3 Postoperative outcome

	Total ($n = 259$)	Mannitol ($n = 188$)	Nonmannitol ($n = 71$)	*p*-Value
POD, *n* (%)	50 (19.3%)	26 (13.8%)	24 (33.8%)	*0.001*
Reintubation	13 (5.1%)	5 (2.7%)	8 (11.3%)	*0.009*
SAPS II score 24 h	29.7 ± 7.2	28.7 ± 7.1	32.2 ± 7.0	*<0.001*
Ventilation time (h)	19.0 ± 33.9	17.1 ± 33.1	24.1 ± 35.6	*0.021*
ICU stay (h)	81.5 ± 147.3	70.0 ± 110.2	112.0 ± 214.7	*0.040*
Readmission to ICU	18 (6.9%)	9 (4.8%)	9 (12.7%)	*0.026*
In-hospital stay postop (d)	14.5 ± 12.8	12.6 ± 9.7	17.8 ± 11.3	*<0.001*
Treatment expenses (€)	17,351 ± 5,168	16,606 ± 3,842	19,349 ± 7,341	*<0.001*
30-d mortality	7 (2.7%)	7 (3.7%)	0 (0.0%)	0.099

Abbreviations: ICU, intensive care unit; Mannitol, patients received mannitol during extracorporeal circulation; Nonmannitol, patients without mannitol treatment; POD, postoperative delirium; postop, postoperative; SAPS II, Simplified Acute Physiology Score II.
Notes: Summary of data on postoperative outcome and adverse events. Values are expressed as mean ± standard deviation, or as number and percentage (in bracket). Significant changes are displayed in italics.

ventilation time, higher reintubation rate, increased ICU readmission rates, and a prolonged ICU and total hospital stay. Accordingly, total treatment expenses were ≈2,700 € higher in nonmannitol patients. Also, absence of mannitol treatment was associated with significantly higher mortality-predicting SAPS II score 24 hours after surgery. In ►**Table 4**, data were examined according to the criterion "delirium": Here, the above-mentioned findings on postoperative outcome are accredited, while TISS-10 score and associated treatment expenses (≈5,000 € higher costs during hospital stay) were significantly higher in patients suffering from POD.

Table 4 Comparison between delirious and nondelirious patients

	Delirium ($n = 50$)	Nondelirium ($n = 209$)	*p*-Value
Pneumonia	14 (28.0%)	7 (3.3%)	*<0.001*
Reintubation	11 (22.0%)	2 (1.0%)	*<0.001*
SAPS II score 24 h	35.0 ± 7.3	28.4 ± 6.7	*<0.001*
TISS-10 24 h	24.6 ± 4.6	19.3 ± 6.8	*<0.001*
Ventilation time (h)	31.6 ± 39.4	16.0 ± 31.8	*<0.001*
ICU stay in h	193.6 ± 234.9	54.6 ± 100.5	*<0.001*
Readmission to ICU	15 (30.0%)	3 (1.4%)	*<0.001*
In-hospital stay postop (d)	20.2 ± 18.9	18.4 ± 76.4	*0.003*
Treatment expenses (€)	21,625 ± 8,733	16,326 ± 3,113	*<0.001*
30-d mortality	1 (2.0%)	6 (2.9%)	0.116

Abbreviations: ICU, intensive care unit; postop, postoperative; SAPS II, Simplified Acute Physiology Score II; TISS, Therapeutic Intervention Scoring System.
Notes: Summary of data on postoperative outcome and adverse events compared between delirious and nondelirious patients. Values are expressed as mean ± standard deviation, or as number and percentage (in bracket). Significant changes are displayed in italics.

In multivariable regression analysis, mannitol was an independent and statistically significant factor associated with lower incidence of POD (►**Table 5**). A visualization of this model using prototypical values is shown in ►**Fig. 1**. A receiver operating characteristics analysis was performed to investigate the discrimination ability of our model. Our model showed an area under the curve of 0.84 (►**Fig. 2**; 95% confidence interval: 0.78–0.91; $p < 0.001$). Recursive partitioning was utilized to investigate and visualize the influence of mannitol on POD and is displayed in ►**Fig. 3**.

Discussion

In this study, we were able to show that mannitol administration during ECC decreases the incidence of POD in patients undergoing AVR. POD is a severe postoperative neurological complication being associated with increased morbidity and mortality, longer hospital stays, and enhanced medical costs.[25–27] Accordingly, we show that nurse workload index TISS-10, mortality predicting SAPS II,[28,29] duration of mechanical ventilation, duration of ICU and hospital stays,

Table 5 Multivariable logistic regression model

Factor	OR	95% CI	*p*-Value
Intercept	0.0061	0.0008–0.0383	*<0.001*
Mannitol substitution	0.4025	0.1815–0.8930	*0.02*
Reintubation	9.0824	1.9884–65.2400	*0.009*
Pneumonia	5.0479	1.4688–17.7855	*0.009*
SAPS II score 24 h	1.0962	1.0381–1.1620	*0.001*
EuroSCORE II	1.6755	1.0754–2.6725	*0.03*

Abbreviations: CI, confidence interval; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; OR, odds ratio; SAPS II, Simplified Acute Physiology Score II.
Notes: Results of the multivariate logistic regression analysis. Significant changes are displayed in italics.

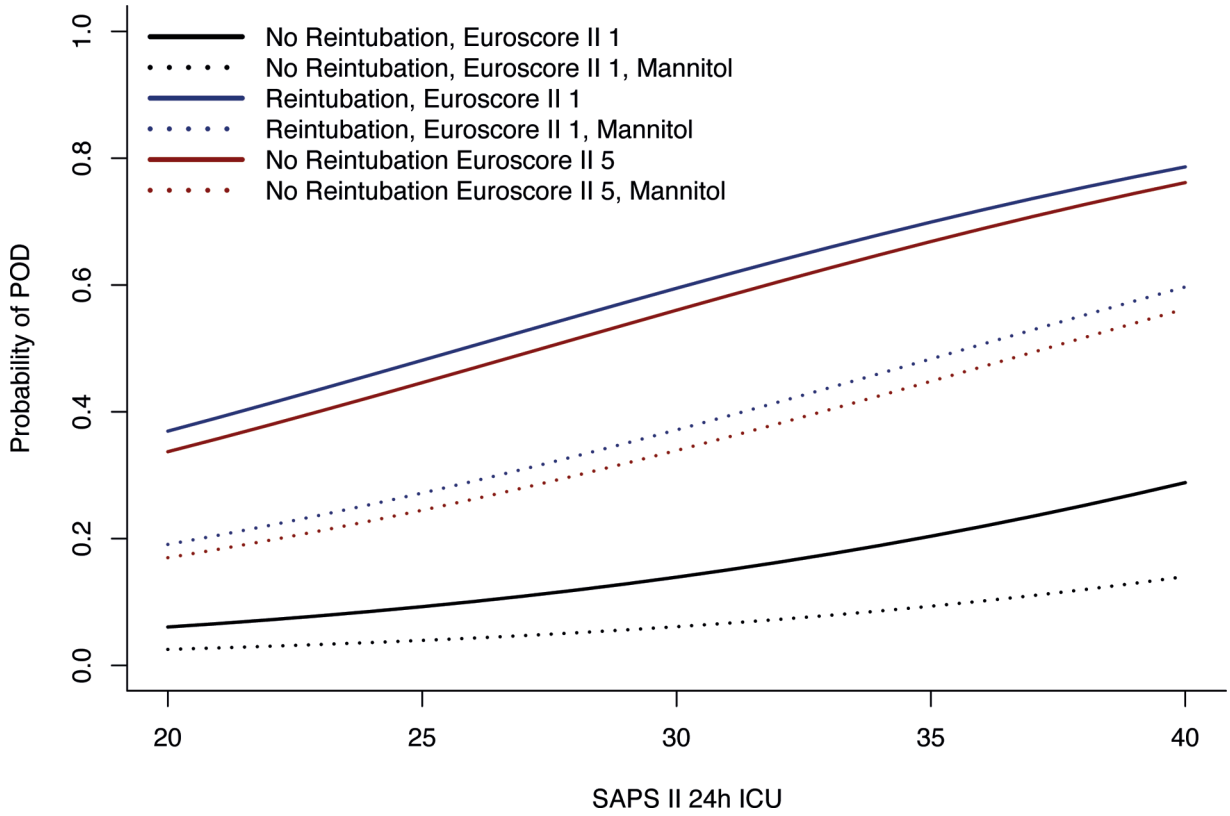

Fig. 1 A visualization of our multivariable model (►**Table 5**) using prototypical values for reintubation, EuroSCORE II, mannitol substitution and SAPS II score. EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; ICU, intensive care unit; POD, postoperative delirium; SAPS II, Simplified Acute Physiology Score II.

readmission to ICU, and incidence for pneumonia were significantly higher in patients suffering from POD after AVR. Further, POD was associated with significantly enhanced medical costs, which has also been reported after major urological surgery.[27] POD, particularly its hypoactive form, is often overlooked during ICU, which could be associated with far-reaching consequences.[30] We applied the CAM-ICU test that has been proven to be suitable for POD screening of postcardiotomy patients.[24] In this regard, early recognition and treatment of POD have been demonstrated to be key for the reduction, duration, and severity of POD with associated negative outcomes.[31]

Various studies have investigated predisposing and precipitating factors of POD in postcardiotomy patients.[32,33] Beside individual patient conditions, procedure-associated factors, such as the complexity of surgery, and consequently, duration of ECC have been identified as independent predisposing factors for postcardiotomy POD.[34,35] Also, besides their association with postoperative renal failure, the use of HES and HA as HLM priming solutions is related to early POD.[18] Although RAP is the standard procedure in many hospitals, the HLM tubing system is primed with crystalloid solution, potentially resulting in a drop in oncotic pressure. With respect to the kidney-related disadvantages of HES, mannitol has been used during ECC for years to maintain an elevated oncotic pressure and a more stable MAP.

While most studies have focused on the effect of mannitol on postoperative renal failure,[36,37] we investigated the impact of mannitol substitution on POD and postoperative outcome in a cohort of postcardiotomy patients undergoing elective AVR. Patients with preexisting mental conditions were excluded. Our data reveal no differences with respect to preoperative demographic characteristics, organ function, coagulation, and inflammation parameters between the mannitol and the non-mannitol groups. Also, EuroSCORE II was not different. Most importantly, we show in multivariable regression analysis that mannitol was an independent and statistically significant factor associated with lower incidence of POD; while POD incidence in nonmannitol patients was in accordance with other studies,[3,33] mannitol supplementation was associated with only 13.8% POD in patients with a comparable ECC and aortic cross-clamping time. A visualization of our model showed significantly lower probability of POD independent of the operative risk stratification of the patient (EuroSCORE II), need for reintubation, development of pneumonia, or SAPS II 24 hours score. Recursive partitioning was utilized to visualize the influence of mannitol on POD, showing that with increasing EuroSCORE II, mannitol treatment is associated with lower incidence of POD. Furthermore, lower incidence of POD in the mannitol group was accompanied by shorter ventilation time, ICU and total hospital stay, lower ICU readmission rate, and reintubation rate and lower SAPS II score. The 30-day mortality was not affected.

Against the background of increasing shortage of health care professionals, identification and elimination of modifiable risk factors and potentially preventing POD in

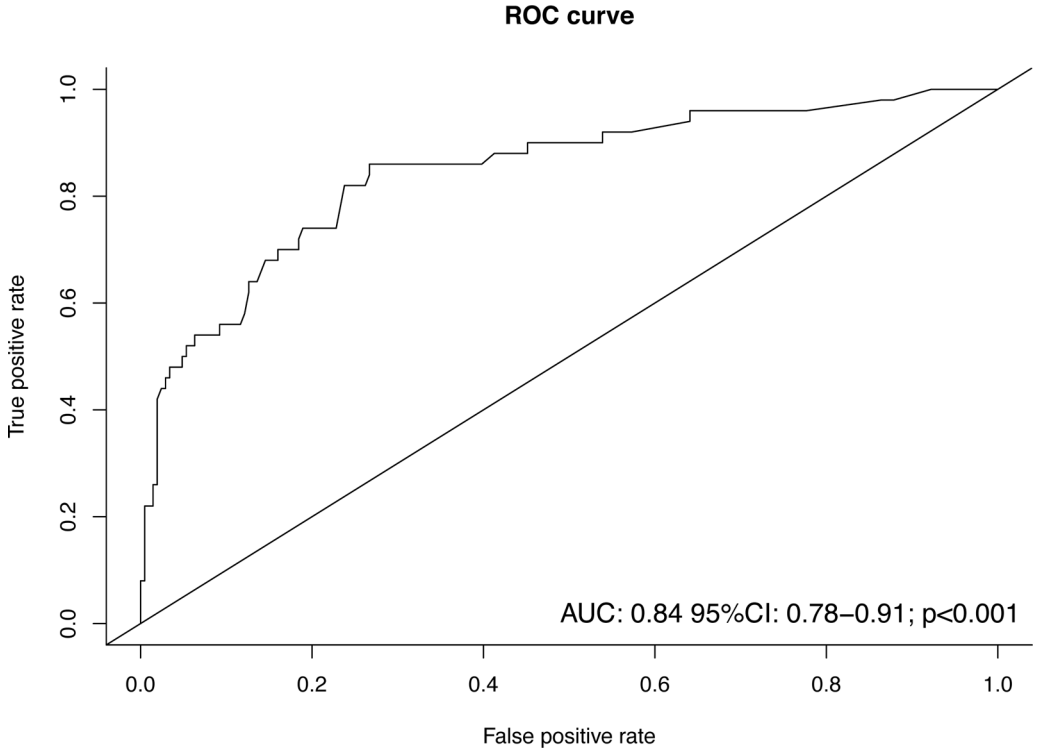

Fig. 2 ROC analysis for delirium and mannitol substitution. The ROC curve and the AUC show a good discrimination ability of our multivariable model (AUC: 0.84; 95% CI: 0.78–0.91; $p < 0.001$). AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

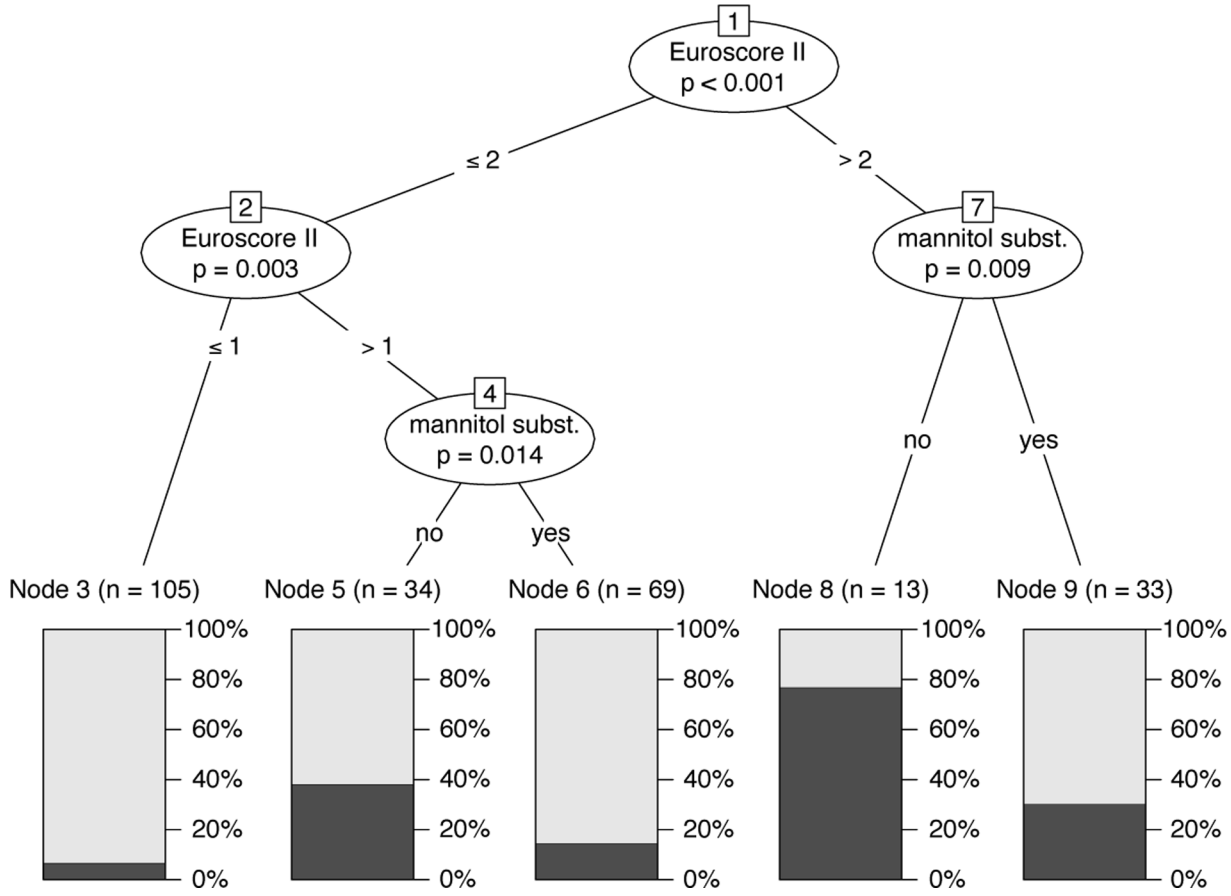

Fig. 3 Recursive partitioning and conditional inference trees. An analysis with recursive partitioning and conditional inference trees showing the influence of mannitol on POD in all EuroSCORE II groups. EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; POD, postoperative delirium.

postcardiotomy patients have a high priority. From the economic perspective, longer ventilation time with prolonged ICU stay causes increased treatment expenses.[5,7,26] Our data are in line with previous studies, connecting POD to longer hospitalization time and higher treatment expenses after major surgeries.[7,27] Moreover, we could show that mannitol substitution was associated with significantly reduced treatment costs. Therefore, our data suggest that patients with no mannitol treatment have a higher probability for development of POD, causing higher need for ICU stay, which in return leads to lower number of surgeries. Besides higher treatment expenses, this potentially contributes to lower earnings of the surgical department.

In the past, effects of mannitol administration during cardiac surgery have been studied focusing on postoperative acute renal failure, showing that mannitol has no effect on renal function during cardiac surgery in patients with or without established renal dysfunction.[36,37] In agreement with this, we did not observe signs of renal failure after mannitol administration, as demonstrated by comparable postoperative maximum serum creatinine values, accompanied by comparable total diuresis and fluid balance after 24 hours in both groups. Also, the trend of serum creatinine as well as the need for CVVH has been similar between the two groups. These data are in line with the above-cited studies showing neither advantage nor disadvantage of mannitol substitution on renal function; also, the effect of mannitol removal from the priming solution based on observations of high volume and potassium requirements resulting from excessive diuresis did not have any effect on electrolytes, fluid status, and other outcomes in another study.[38]

Furthermore, a potential role of the sodium shift induced by Bretschneider solution for induction of POD by inducing an acute hyponatremia has to be considered, as Aldemir et al reported that hyponatremia is a predicting factor for delirium in a surgical ICU.[39] In this regard, univariable and multivariable logistic regression showed that both mean and minimum serum sodium concentration during CPB were not independently associated with incidence of POD in our study. This suggests that the use of hyponatremic Bretschneider cardioplegic solution has no impact on prevalence of POD.

With respect to possible underlying mechanisms, it is known that CPB promotes systemic inflammatory response syndrome due to activation of the complement system, resulting in a reaction including cytokines release, leukocyte activation, and ROS generation.[40] This cascade leads to endothelial dysfunction leading to interstitial edema. This may disrupt the blood–brain barrier and result in neuroinflammation with activation of microglial cells.[41] Neuroinflammation itself leads to fluid accumulation and swelling, favoring POD.[42] Here, this mechanistic concept of mannitol use to reduce cell edema could be transferred to cardiac surgery. Further, it has been shown that mannitol reduces the plasma levels of ROS,[43] and reportedly, antioxidant therapy with mannitol during CPB induced immunosuppression after coronary artery bypass graft surgery.[22] In this light, mannitol might also exert its antidelirious effect via suppression of neuroinflammation. But an examination of the underlying mechanisms of mannitol treatment and its connection to POD were beyond the scope of this study.

In summary, our data suggest that mannitol supplementation should be considered in patients undergoing CPB. However, the appropriate dosage should be accredited in patients with impaired renal function.

Limitation of the Study

Our study is limited due to its retrospective character, resulting in unequally sized patient groups. An additional limitation of the study is the lack of preoperative cognitive assessment and evaluation of preoperative delirium using common confusion assessment methods such as the Montreal Confusion Assessment or Mini-Mental Test. In addition, we do not provide data on postoperative quality of life. Regarding the use of Bretschneider cardioplegic solution and associated intraoperative hyponatremia during CPB, we acknowledge that the beneficial effects of mannitol may not be observed in patients treated with modern blood cardioplegia solutions (e.g., Buckberg, Calafiore, etc.). Therefore, any conclusions will need to be proven by a randomized controlled trial.

Conclusion

Early recognition of POD is important since it is associated with worse postoperative outcome, prolonged ICU and hospital stay, and thus higher treatment expenses. Our study shows for the first time that supplementation with mannitol during ECC is associated with lower incidence of POD in elective AVR. The 30-day mortality and other serious postoperative complications, especially renal failure, were comparable. Considering mannitol use during CPB could lead to less POD and might result in significant cost savings.

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Conflict of Interest

None declared.

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M. Hamiko and E.I. Charitos contributed equally to the manuscript; M. Hamiko was mainly involved in the preparation of the data and drafting of the manuscript, while E. I. Charitos performed the statistical analysis and was involved in study design.

References

1 Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. J Card Surg 2012;27(04): 481–492

2 Rudolph JL, Jones RN, Levkoff SE, et al. . Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation 2009;119(02):229–236

3 Burkhart CS, Dell-Kuster S, Gamberini M, et al. . Modifiable and nonmodifiable risk factors for postoperative delirium after

cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2010;24(04):555–559
4 Lat I, McMillian W, Taylor S, et al. . The impact of delirium on clinical outcomes in mechanically ventilated surgical and trauma patients. Crit Care Med 2009;37(06):1898–1905
5 Ely EW, Shintani A, Truman B, et al. . Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291(14):1753–1762
6 Rudolph JL, Inouye SK, Jones RN, et al. . Delirium: an independent predictor of functional decline after cardiac surgery. J Am Geriatr Soc 2010;58(04):643–649
7 Milbrandt EB, Deppen S, Harrison PL, et al. . Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004; 32(04):955–962
8 Zaubler TS, Murphy K, Rizzuto L, et al. . Quality improvement and cost savings with multicomponent delirium interventions: replication of the Hospital Elder Life Program in a community hospital. Psychosomatics 2013;54(03):219–226
9 O'Neal JB, Billings FT IV, Liu X, et al. . Risk factors for delirium after cardiac surgery: a historical cohort study outlining the influence of cardiopulmonary bypass. Can J Anaesth 2017;64(11): 1129–1137
10 Scott TR, Kronsten VT, Hughes RD, Shawcross DL. Pathophysiology of cerebral oedema in acute liver failure. World J Gastroenterol 2013;19(48):9240–9255
11 Sirs JA, Glenville B, Stanbridge RL, et al. . The influence of vascular pressure and different primes on the fluid balance of, and oxygen supply to, the patient during CABG. Perfusion 1995; 10(01):33–44
12 Russell JA, Navickis RJ, Wilkes MM. Albumin versus crystalloid for pump priming in cardiac surgery: meta-analysis of controlled trials. J Cardiothorac Vasc Anesth 2004;18(04):429–437
13 Himpe D. Colloids versus crystalloids as priming solutions for cardiopulmonary bypass: a meta-analysis of prospective, randomised clinical trials. Acta Anaesthesiol Belg 2003;54(03):207–215
14 Weiler P, Hamiko M, Mellert F, et al. . Impact of crystalloid or albumin priming of the heart-lung machine on inhospital outcome after coronary artery bypass surgery. Thorac Cardiovasc Surg 2019;67(06):475–483
15 Svendsen OS, Farstad M, Mongstad A, Haaverstad R, Husby P, Kvalheim VL. Is the use of hydroxyethyl starch as priming solution during cardiac surgery advisable? A randomized, single-center trial. Perfusion 2018;33(06):483–489
16 Frenette AJ, Bouchard J, Bernier P, et al. . Albumin administration is associated with acute kidney injury in cardiac surgery: a propensity score analysis. Crit Care 2014;18(06):602
17 Lee EH, Kim WJ, Kim JY, et al. . Effect of exogenous albumin on the incidence of postoperative acute kidney injury in patients undergoing off-pump coronary artery bypass surgery with a preoperative albumin level of less than 4.0 g/dl. Anesthesiology 2016;124(05):1001–1011
18 Jung DM, Ahn HJ, Yang M, et al. . Hydroxyethyl starch is associated with early postoperative delirium in patients undergoing esophagectomy. J Thorac Cardiovasc Surg 2018;155(03):1333–1343
19 Nau R. Osmotherapy for elevated intracranial pressure: a critical reappraisal. Clin Pharmacokinet 2000;38(01):23–40
20 Poullis M. Mannitol and cardiac surgery. Thorac Cardiovasc Surg 1999;47(01):58–62
21 Ljunggren M, Sköld A, Dardashti A, Hyllén S. The use of mannitol in cardiopulmonary bypass prime solution-prospective randomized double-blind clinical trial. Acta Anaesthesiol Scand 2019;63 (10):1298–1305
22 Ziegeler S, Raddatz A, Schneider SO, et al. . Effects of haemofiltration and mannitol treatment on cardiopulmonary-bypass induced immunosuppression. Scand J Immunol 2009;69(03):234–241
23 Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: classification and criteria changes. World Psychiatry 2013;12(02):92–98
24 Guenther U, Popp J, Koecher L, et al. . Validity and reliability of the CAM-ICU flowsheet to diagnose delirium in surgical ICU patients. J Crit Care 2010;25(01):144–151
25 Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med 2009; 180(11):1092–1097
26 Thomason JW, Shintani A, Peterson JF, Pun BT, Jackson JC, Ely EW. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. Crit Care 2005;9(04):R375–R381
27 Ha A, Krasnow RE, Mossanen M, et al. . A contemporary population-based analysis of the incidence, cost, and outcomes of postoperative delirium following major urologic cancer surgeries. Urol Oncol 2018;36(07):341.e15–341.e22
28 Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270(24):2957–2963
29 Miranda DR, de Rijk A, Schaufeli W. Simplified Therapeutic Intervention Scoring System: the TISS-28 items–results from a multicenter study. Crit Care Med 1996;24(01):64–73
30 Yang FM, Marcantonio ER, Inouye SK, et al. . Phenomenological subtypes of delirium in older persons: patterns, prevalence, and prognosis. Psychosomatics 2009;50(03):248–254
31 Eden BM, Foreman MD. Problems associated with underrecognition of delirium in critical care: a case study. Heart Lung 1996; 25(05):388–400
32 Kazmierski J, Kowman M, Banach M, et al; IPDACS Study. Incidence and predictors of delirium after cardiac surgery: results from The IPDACS Study. J Psychosom Res 2010;69(02):179–185
33 Guenther U, Theuerkauf N, Frommann I, et al. . Predisposing and precipitating factors of delirium after cardiac surgery: a prospective observational cohort study. Ann Surg 2013;257(06): 1160–1167
34 Bakker RC, Osse RJ, Tulen JH, Kappetein AP, Bogers AJ. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. Eur J Cardiothorac Surg 2012;41(03):544–549
35 van der Mast RC, van den Broek WW, Fekkes D, Pepplinkhuizen L, Habbema JD. Incidence of and preoperative predictors for delirium after cardiac surgery. J Psychosom Res 1999;46(05): 479–483
36 Smith MN, Best D, Sheppard SV, Smith DC. The effect of mannitol on renal function after cardiopulmonary bypass in patients with established renal dysfunction. Anaesthesia 2008; 63(07):701–704
37 Yallop KG, Sheppard SV, Smith DC. The effect of mannitol on renal function following cardio-pulmonary bypass in patients with normal pre-operative creatinine. Anaesthesia 2008;63(06):576–582
38 Haydock MD, Kruger C, Willcox T, Haydock DA. Does removing Mannitol and Voluven from the priming fluid of the cardiopulmonary bypass circuit have clinical effects? J Extra Corpor Technol 2014;46(01):77–83
39 Aldemir M, Ozen S, Kara IH, Sir A, Baç B. Predisposing factors for delirium in the surgical intensive care unit. Crit Care 2001;5(05): 265–270
40 Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. Chest 1997;112(03):676–692
41 Rudolph JL, Ramlawi B, Kuchel GA, et al. . Chemokines are associated with delirium after cardiac surgery. J Gerontol A Biol Sci Med Sci 2008;63(02):184–189
42 Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. Acta Neuropathol 2010;119(06):737–754
43 Ferreira R, Burgos M, Llesuy S, et al. . Reduction of reperfusion injury with mannitol cardioplegia. Ann Thorac Surg 1989;48(01): 77–83, discussion 83–84