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Perioperative blood pressure variability as a risk factor for postoperative delirium in the patients receiving cardiac surgery

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Abstract

Background Delirium is one of the most common neurological complications after cardiac surgery. The purpose of our study was to assess the relationship between perioperative blood pressure variability (BPV) and postoperative delirium (POD) in the patients undergoing cardiac surgery.

Methods Adult patients received cardiac surgery and stayed in Cardiovascular Intensive Care Unit (ICU) for more than 24 h after surgery during the study period between June 2019 and December 2022 were included in this study. Baseline characteristics, perioperative hemodynamic variables and postoperative laboratory results of the cardiac patients were collected and analyzed. Perioperative BPV was quantified by calculating the standard deviation (SD) and average real variability (ARV) of blood pressure. Assessment of delirium was based on the mental status of the patients and CAM-positive. The relationship between perioperative BPV and POD was analyzed by LASSO and logistic regression using R (R package, 4.3.2).

Results The incidence of POD was 15.0% (324/2164) in the patients receiving cardiac surgery, and the average day for POD occurred at day 3 after surgery. Patients with POD had statistically lower levels of intraoperative mean blood pressure ($P=0.015$) and blood pressure ARV ($P<0.001$) as well as mean blood pressure at 24 h postoperatively ($P=0.003$) when compared to those without. Whereas, ARV for systolic blood pressure (8.64 vs. 7.91 mmHg, $P<0.001$), diastolic blood pressure (4.00 vs. 3.77 mmHg, $P=0.014$) and mean blood pressure (5.23 vs. 4.94 mmHg, $P=0.001$) at 24 h postoperatively was significantly higher in the patients with POD than those without. LASSO regression and further logistic regression revealed that intraoperative blood pressure ARV (OR:0.92, $P<0.001$), mean central venous pressure (OR:1.05, $P=0.048$) and ARV of systolic blood pressure (OR:1.17, $P=0.002$) at 24 h postoperatively were independent risk factors for POD.

Conclusions Perioperative ARV, especially postoperative high ARV exposure, was associated with POD in the patients receiving cardiac surgery. Maintaining a relatively stable blood pressure after cardiac surgery might be beneficial to avoid POD in those patients.

Keywords Blood pressure variability, Postoperative delirium, Neurological complication, Cardiac surgery

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Introduction

Delirium, manifested by disturbance of consciousness, irregular behavior, and inability to concentrate, is one of the most common postoperative complications in both cardiac patients and non-cardiac patients [1]. In cardiac patients, delirium is the most common neurological complications after cardiac surgery, leading to prolonged length of Intensive Care Unit (ICU) stay and hospital stay, as well as increased mortality [2]. Causes of postoperative delirium (POD) in the cardiac surgery may attribute to the use of anesthetic agents, the infection secondary to surgery procedure and cardiopulmonary bypass (CPB), inflammation, etc. [3, 4].

Several studies have investigated the risk factors for POD in cardiac patients. A meta-analysis revealed the following risk factors for POD after cardiac surgery, including age, New York Heart Association (NYHA) functional class III or IV, preoperative depression, co-morbidities of mild cognitive impairment, diabetes and carotid artery stenosis, duration of mechanical ventilation as well as length of ICU stay [5]. However, current studies mainly focused on the baseline characteristics, surgery time and postoperative laboratory variables of the cardiac patients, studies on the influence of perioperative hemodynamic variables for POD were rare.

Recent studies dedicated to clarify the correlation between blood pressure and delirium. A post-hoc analysis for DECADE trial assessed the association between perioperative hypotension and POD after cardiac surgery and found that neither intraoperative nor postoperative hypotension were associated with delirium [6]. Whereas, blood pressure variability (BPV) was found to be associated with delirium in certain populations [7, 8]. A retrospective study by Zorko et al. revealed that BPV in the first 24 h after ICU admission was associated with an increased likelihood of delirium in the critically ill patients [9]. Another pilot study assessed the optimal mean arterial pressure (MAP) by cerebral blood flow autoregulation using ultrasound-tagged near-infrared spectroscopy during CPB procedure and the first 3 h after surgery in 110 cardiac patients [8]. This study found that the incidence and severity of delirium on postoperative day 2 was associated with excursions above the optimal MAP. Whereas, studies on the correlations between BPV and POD in the cardiac patients were insufficient.

Therefore, the purposes of our study were: 1) to investigate the association between perioperative hemodynamic variables and POD in the patients undergoing on-pump cardiac surgery; 2) to assess the relationship between perioperative BPV and POD in the cardiac patients.

Material and methods

This study was a retrospective, case–control study performed at the Cardiovascular Intensive Care Unit (CVICU) of Nanjing First Hospital, a tertiary teaching hospital affiliated to Nanjing Medical University. The study was approved by the Ethics Committee of Nanjing First Hospital, Nanjing Medical University (KY20220518-01-KS-01) with a waiver of the requirement for informed consent.

Patient population

Adult cardiac patients (aged $\geq$ 18 years old) that received cardiac surgery and admitted to CVICU after surgery during the study period between June 2019 and December 2022 were screened for potential analysis. Those who underwent CPB procedure and received invasive blood pressure and central venous pressure (CVP) monitoring during and after surgery were included in this study. Patients were excluded from the study if they met the following criteria: 1) died during and within 48 h after surgery; 2) admitted to ICU before surgery; 3) stayed in ICU for less than 24 h after cardiac surgery; 4) received allograft orthotopic heart transplantation; 5) unable to communicate due to preexisting stroke, dementia, and other brain diseases; 6) were receiving the therapy of psychotropic drugs before surgery; 7) complicated with stroke after surgery; 8) with missing data in hemodynamic variables, medical records, and CAM-ICU evaluation during and after surgery.

Data collection

Baseline characteristics of the cardiac patients included gender, age, body mass index (BMI), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, European System for Cardiac Operative Risk Evaluation (euroSCORE) score and co-morbidities (medical history of stroke, hypertension, diabetes mellitus, coronary artery disease [CAD], chronic renal failure [CRF], atrial fibrillation [AF], chronic obstructive pulmonary disease [COPD], etc.) were obtained and analyzed.

Intraoperative blood pressure measurement was continuous via invasive arterial pressure monitoring during the procedure of cardiac surgery, and the values were recorded every five minutes in the anesthesia system (DoCare). Central venous pressure (CVP) was also measured continuously via central vein or pulmonary artery catheter monitoring during the procedure of cardiac surgery and the values were recorded every five minutes. Other intraoperative variables including surgery types, surgery time, CPB time, aortic cross-clamp time and fluid balance were also recorded.

Postoperative blood pressure measurement was continuous via invasive arterial pressure monitoring after cardiac surgery during ICU stay, and the values were recorded every 30 min in the electronic medical records (EMR) database. CVP was also measured continuously after cardiac surgery during ICU stay, and the values were recorded every 30 min. Other hemodynamic variables including heart rate (HR) and pulse oxygen saturation (SpO_2) were also continuously measured by ECG monitoring and recorded every 30 min. Postoperative hemodynamic variables including HR, blood pressure (BP, including systolic blood pressure [IBPs], diastolic blood pressure [IBPd] and mean blood pressure [IBPm]), CVP and SpO_2 during the first 24 h after cardiac surgery were obtained and analyzed in this study. Furthermore, postoperative laboratory results at ICU admission, maximum doses of inotropic drugs within the first 24 h after ICU admission and requirement for mechanical-assisted circulation including intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO) were also collected and analyzed. In addition, prognostic indexes including mechanical ventilation time, length of ICU stay and hospital stays, hospital mortality, incidence of acute kidney injury (AKI) and requirement for renal replacement therapy (RRT) were also recorded for analysis.

Delirium assessment

Assessment of delirium was routinely performed by the nurses twice a day during ICU stay, and as needed after ICU discharge using confusion assessment method for ICU (CAM-ICU). First of all, the consciousness levels of the patients were assessed by Richmond Agitation-Sedation scale (RASS). After that, the mental status of the patients was evaluated with CAM-ICU in those patients with RASS score ≥ -3. The diagnosis of delirium was mainly based on the mental status of the patients. There were four characteristics of delirium diagnosis in CAM-ICU: ① acute change or fluctuation of mental state; ② Lack of concentration; ③ Disorder of thinking; ④ Changes in the level of consciousness. The patients were diagnosed with delirium when they met the characteristics of ①, ② and ③ or ④ [10].

Calculation of BPV

Intraoperative blood pressure (mean blood pressure) was recorded every five minutes during the operation and postoperative blood pressure (IBPs, IBPd and IBPm) was recorded every 30 min for the first 24 h after cardiac surgery during ICU stay. Systolic blood pressure below 40 mmHg or above 300 mmHg and diastolic blood pressure below 20 mmHg or above 150 mm Hg were set to missing and excluded from analysis. BPV was quantified by calculating the standard deviation (SD) and average real variability (ARV) of blood pressure.

The calculation formula of SD was according to the following formula as previously reported [11]:

$$SD = \sqrt{(\sum_{i=1}^{n} (x_i - \bar{x})^2)/n - 1}$$

x_i: blood pressure at different time point, $\bar{x}$: mean value of blood pressure, n: number of blood pressure measurements.

ARV of blood pressure was calculated based on the calculation formula that was reported in the literature and listed as follows [12]:

$$ARV = \sum_{i=1}^{n-1} (x_{i+1} - x_i)/n - 1$$

x_i: blood pressure at different time point, x_{i+1}: blood pressure at next time point, n: number of blood pressure measurements.

Statistical analysis

R statistical software (R version 4.3.2) was used for statistical analysis in this study. Continuous variables were expressed as mean plus SD for those conforming to normal distribution and median plus interquartile range (IQR) for those not conforming to normal distribution. Independent-sample T test was preformed to compare the difference in the two groups for continuous variables conforming to normal distribution. For continuous variables not conforming to normal distribution, Mann–Whitney U-test was carried out to compare the difference between the two groups. Categorical variables were presented as absolute values plus proportions analyzed by Chi-square test. The Least absolute shrinkage and selection operator (LASSO) regression was adopted to screen the potential hemodynamic variables contributing to the occurrence of POD. Afterwards, multivariate logistic regression was performed and logistic regression forest plot was drawn based on the hemodynamic variables screened by LASSO analysis. Furthermore, Restricted cubic spline (RCS) analysis was performed to assess the nonlinear associations between BPV and POD after cardiac surgery. Statistically significance was considered as a two-sided $P < 0.05$.

Results

Four thousand four hundred ninety cardiac patients who received cardiac surgery and admitted to CVICU after surgery during the study period between June 2019 and December 2022 were screened. Finally, 2164 patients were included and analyzed in our study (Fig. 1). Of all the study patients, the incidence of POD was15.0%

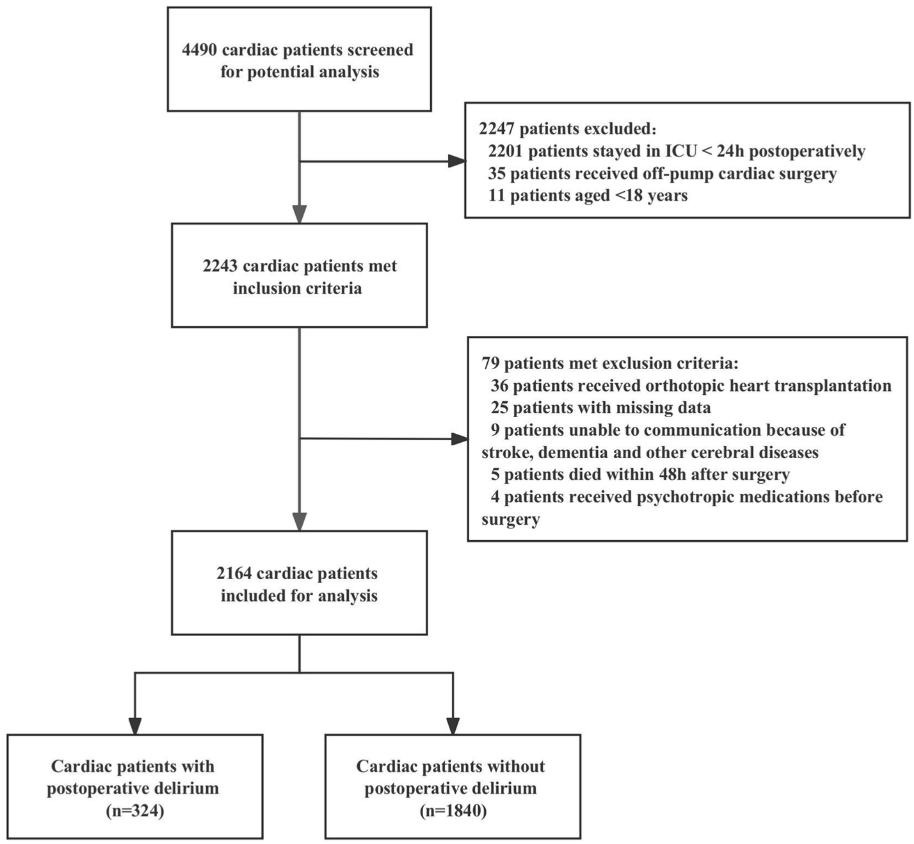

Fig. 1 Screening flowchart of the study patients. ICU: Intensive Care Unit

(324/2164), and the average day for POD occurred at day 3 (1, 5) after surgery. Patients were divided into two groups based on the occurrence of POD: Delirium group ($n = 324$) and No Delirium group ($n = 1840$).

Comparison of baseline characteristics

The comparison of baseline characteristics of the patients in the two groups were presented in Table 1. Cardiac patients in the delirium group were predominantly male (237 [73.1%] vs. 1060 [57.6%], $P < 0.001$), with older age (69 [61, 74] vs. 65 [57, 71] years, $P < 0.001$), higher APACHE II score (14 [12, 17] vs. 12 [10, 15], $P < 0.001$) and euroSCORE (6 [5, 8] vs. 5 [4, 7], $P < 0.001$). Moreover, patients with co-morbidities of CAD and CRF were more likely to suffer POD when compared to those without. In terms of surgery type, cardiac patients in the delirium group had a significantly higher proportion to receive combined surgery of valve replacement/repair and coronary artery bypass grafting (CABG) and acute Stanford Type A aortic dissection (AAAD) surgery. In addition, patients in the delirium group had markedly longer operation time (290 [249, 340] vs. 260 [220, 310] min, $P < 0.001$), CPB time (128 [101, 167] vs. 115 [88, 147] min, $P < 0.001$) and aortic cross-clamp time (85.5 [67, 114] vs. 78 [59, 103] min, $P < 0.001$). Besides, patients in delirium group received higher doses of inotropic drugs within 24 h after cardiac surgery when compared with those in no delirium group.

In the aspect of prognostic indexes, cardiac patients in delirium group were more likely to have prolonged time for mechanical ventilation (20.2 [13.3, 44.8] vs. 13.3 [8.8, 19.3] min, $P < 0.001$), longer duration of ICU stay (4 [2, 6] vs. 2 [2, 3] d, $P < 0.001$) and hospital stay (21 [17, 28] vs. 18 [15, 22] d, $P < 0.001$), as well as higher hospital mortality (29 [8.95%] vs. 50 [2.72%], $P < 0.001$).

Comparison of perioperative hemodynamic variables

To evaluate the association between perioperative hemodynamic variables and POD, we compared the perioperative hemodynamic variables in the two groups (Supplementary Table 1). Patients in delirium group had lower levels of intraoperative mean blood pressure (BP_mean, 64 [59, 67] vs. 64 [60, 68] mmHg, $P = 0.015$) and blood pressure ARV (BP_arv, 8.52 [6.40, 10.2] vs. 8.94 [7.08, 11.5] mmHg, $P < 0.001$) when compared to those in no delirium group.

Table 1 Baseline characteristics of the cardiac patients with or without postoperative delirium

Variables	No Delirium (*n* = 1840)	Delirium (*n* = 324)	*P* value
Male, n (%)	1060 (57.6%)	237 (73.1%)	< 0.001
Age, years	65 [57;71]	69 [61;74]	< 0.001
BMI, kg/m^2	20.2 [19.0;21.5]	20.0 [18.8;22.0]	0.196
APACHE II score	12 [10;15]	14 [12;17]	< 0.001
EuroSCORE	5 [4;7]	6 [5;8]	< 0.001
Co-morbidities, n (%)			
Stroke	250 (13.6%)	50 (15.4%)	0.424
Hypertension	901 (49.0%)	171 (52.8%)	0.228
Diabetes mellitus	418 (22.7%)	83 (25.6%)	0.285
CHD	832 (45.2%)	190 (58.6%)	< 0.001
CRF	92 (5.00%)	40 (12.3%)	< 0.001
AF	465 (25.3%)	68 (21.0%)	0.114
COPD	99 (5.38%)	18 (5.56%)	1.000
Surgery types, n (%)			
CABG	539 (29.3%)	108 (33.3%)	0.162
Valve surgery	780 (42.4%)	93 (28.7%)	< 0.001
Combined surgery of valve and CABG	215 (11.7%)	58 (17.9%)	0.003
Aortic surgery	173 (9.40%)	33 (10.2%)	0.734
AAAD	48 (2.61%)	24 (7.41%)	< 0.001
Other surgery	84 (4.57%)	8 (2.47%)	0.115
Intra-operative variables			
Operation time, min	260 [220;310]	290 [249;340]	< 0.001
CPB time, min	115 [88;147]	128 [101;167]	< 0.001
Aortic cross-clamp time, min	78 [59;103]	85.5 [67;114]	< 0.001
Fluid input, ml	2000 [1500;2131]	2000 [1500;2500]	0.001
Blood input, ml	1250 [1000;1561]	1396 [1042;1752]	< 0.001
Fluid output, ml	2000 [1600;2500]	2100 [1688;2555]	0.140
Blood loss, ml	1100 [1000;1300]	1200 [1000;1500]	< 0.001
Urine output, ml	800 [560;1250]	800 [500;1200]	0.084
Fluid balance, ml	−100 [−622;350]	0 [−550;400]	0.220
Maximum doses of inotropic drugs within 24 h after surgery			
Norepinephrine, ug/kg/min	0.00 [0.00;0.10]	0.08 [0.00;0.18]	< 0.001
Dopamine, ug/kg/min	0.00 [0.00;4.00]	0.00 [0.00;3.25]	0.254
Dobutamine, ug/kg/min	0.00 [0.00;3.00]	0.00 [0.00;4.00]	0.055
Epinephrine, ug/kg/min	0.00 [0.00;0.01]	0.00 [0.00;0.04]	< 0.001
Milrinone, ug/kg/min	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.101
Olprinone, ug/kg/min	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.307
Levosimendan, ug/kg/min	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.001
Hypophysin, U/h	0.00 [0.00;0.00]	0.00 [0.00;0.00]	< 0.001
VISmax	7.00 [3.00;15.0]	12.0 [5.00;24.0]	< 0.001
Mechanical ventilation time, h	13.3 [8.8;19.3]	20.2 [13.3;44.8]	< 0.001
Length of ICU stay, d	2 [2;3]	4 [2;6]	< 0.001
Length of hospital stay, d	18 [15;22]	21 [17;28]	< 0.001
Hospital mortality, n (%)	50 (2.72%)	29 (8.95%)	< 0.001
Re-intubation, n (%)	74 (4.02%)	57 (17.6%)	< 0.001
AKI, n (%)	585 (31.8%)	164 (50.8%)	< 0.001
RRT requirement, n (%)	42 (2.28%)	21 (6.48%)	< 0.001
Requirement of MCS, n (%)			
IABP	49 (2.66%)	31 (9.57%)	< 0.001
ECMO	2 (0.11%)	3 (0.93%)	0.026

BMI Body mass index, *APACHE II* Acute Physiology, Age, Chronic Health Evaluation II, *EuroSCORE* European system for cardiac operative risk evaluation, *CHD* Coronary heart disease, *CRF* Chronic renal failure, *AF* Atrial fibrillation, *COPD* Chronic obstructive pulmonary disease, *CABG* Coronary Artery Bypass Grafting, *AAAD* Acute Stanford Type A Aortic Dissection, *CPB* Cardiopulmonary bypass, *VIS* Vasoactive-inotropic score, *ICU* Intensive care unit, *AKI* Acute kidney injury, *RRT* Renal replacement therapy, *MCS* Mechanical circulatory support, *IABP* Intra-aortic balloon pump, *ECMO* Extracorporeal membrane oxygenation

Whereas, postoperative ARV of systolic blood pressure (8.64 [7.32, 10.2] vs. 7.91 [6.57, 9.43] mmHg, $P<0.001$), diastolic blood pressure (4.00 [3.17, 4.83] vs. 3.77 [3.11, 4.60] mmHg, $P=0.014$) and mean blood pressure (5.23 [4.46, 6.19] vs. 4.94 [4.11, 5.94] mmHg, $P=0.001$) at 24 h after surgery was significantly higher in the patients with POD than those without.

Perioperative BPV in predicting POD

LASSO regression of the perioperative variables in predicting POD found that intraoperative BP_65_time (time of blood pressure below 65 mmHg during operation), BP_60_time (time of blood pressure below 60 mmHg during operation) and BP_arv, and mean perfusion pressure (MPP) at 6 h, 12 h postoperatively, mean CVP at 24 h postoperatively as well as ARV of systolic blood pressure and mean blood pressure at 24 h postoperatively were closely associated with POD (Fig. 2). Further logistic regression revealed that BP_arv (OR:0.92, 95%CI: 0.89–0.96, $P<0.001$), mean CVP at 24 h postoperatively (OR:1.05, 95%CI: 1.00–1.10, $P=0.048$) and ARV of systolic blood pressure at 24 h postoperatively (OR:1.17, 95%CI: 1.06–1.30, $P=0.002$) were independent risk factors for POD (Table 2 and Fig. 3). RCS analysis revealed that, the cut-off values for BP_arv and ARV of systolic blood pressure at 24 h postoperatively were 5.640 mmHg and 5.087 mmHg, respectively (Fig. 4).

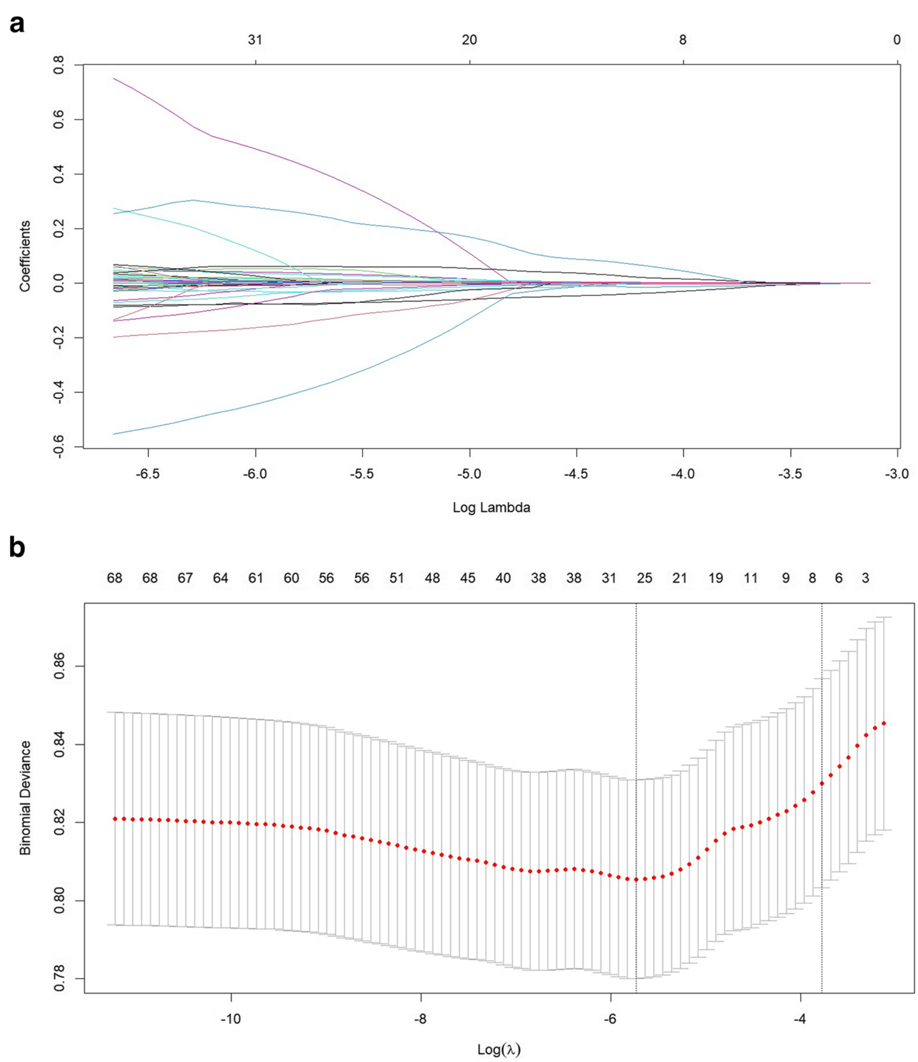

Fig. 2 Selection of perioperative hemodynamic variables contributing to postoperative delirium using the Least absolute shrinkage and selection operator (LASSO) regression method. **A** Plot of LASSO coefficient profiles of the 68 variables. The log (lambda) sequence was plotted against a coefficient profile plot. There were 8 variables with non-zero coefficients generated by the ideal lambda; (**B**) tenfold cross-validation for LASSO model parameter adjustment. The binomial deviation curve was displayed with log (lambda). The minimum criteria and its one standard error were used to construct dotted vertical lines at the optimal values (the 1-SE criteria)

Table 2 Logistic regression for postoperative delirium in the patients receiving cardiac surgery

Dependent: Delirium		No	Yes	OR (univariable)	OR (multivariable)
BP_65_time	Mean (SD)	135.5 (64.1)	158.0 (68.5)	1.00 (1.00–1.01, $p<0.001$)	1.00 (0.99–1.00, $p=0.794$)
BP_60_time	Mean (SD)	99.2 (54.7)	118.2 (60.9)	1.01 (1.00–1.01, $p<0.001$)	1.00 (1.00–1.01, $p=0.287$)
BP_arv	Mean (SD)	9.7 (3.7)	8.7 (3.1)	0.92 (0.88–0.95, $p<0.001$)	0.92 (0.89–0.96, $p<0.001$)
PM_MPP_6h_mean	Mean (SD)	69.2 (7.5)	66.6 (8.6)	0.96 (0.94–0.97, $p<0.001$)	0.99 (0.96–1.03, $p=0.749$)
PM_MPP_12h_mean	Mean (SD)	70.5 (7.0)	68.2 (8.0)	0.96 (0.94–0.97, $p<0.001$)	0.97 (0.93–1.01, $p=0.178$)
PM_CVPm_24h_mean	Mean (SD)	8.0 (2.5)	8.7 (2.9)	1.11 (1.06–1.16, $p<0.001$)	1.05 (1.00–1.10, $p=0.048$)
PM_IBPs_24h_arv	Mean (SD)	8.1 (2.3)	10.6 (33.0)	1.12 (1.06–1.17, $p<0.001$)	1.17 (1.06–1.30, $p=0.002$)
PM_IBPm_24h_arv	Mean (SD)	5.1 (1.5)	5.4 (1.5)	1.11 (1.03–1.20, $p=0.006$)	0.97 (0.82–1.13, $p=0.714$)

OR Odds ratio, *BP* Blood pressure, *BP_65_time* Time of BP < 65 mmHg, *BP_60_time* Time of BP < 60 mmHg, *arv* Average real variability, *MPP* Mean perfusion pressure, *CVP* Central venous pressure, *IBPs* Systolic blood pressure, *IBPm* Mean blood pressure

Discussion

We retrospectively included 2164 cardiac patients in this study and assessed the association between perioperative hemodynamic variables and the occurrence of POD after cardiac surgery. Our study found that, the incidence of POD was 15.0% in the cardiac patients receiving cardiac surgery, which was familiar to other studies [13]. Perioperative ARV rather than hypotension was closely related to POD. A low level of ARV during operation and a high level of ARV after surgery were associated with POD in the cardiac patients.

Our study revealed an association between a low level of ARV during operation and POD in the cardiac patients. The patients we included in this study were all the cardiac patients receiving CPB procedure. Therefore, the patients would experience a period of relatively constant blood pressure during the process of CPB, leading to a low ARV. As a result, ARV during operation may be greatly affected by CPB time. A longer CPB time would lead to a lower ARV during the operation. Consistently, cardiac patients that suffered POD had a significantly longer CPB time (128 min vs. 115 min, $P<0.001$) when compared to those did not. Longer CPB time have been recognized as one of the independent risk factors for POD in the cardiac surgery in numerous studies [14–17], which is consistent with our results.

Recent studies have revealed a relationship between ARV and delirium in critically ill patients. A retrospective observational study by Garbajs et al. found that ARV in the first 24 h after ICU admission was associated with a higher burden of delirium during hospitalization [7]. In the surgical patients, perioperative ARV was also identified as an independent risk factor for POD in non-cardiac

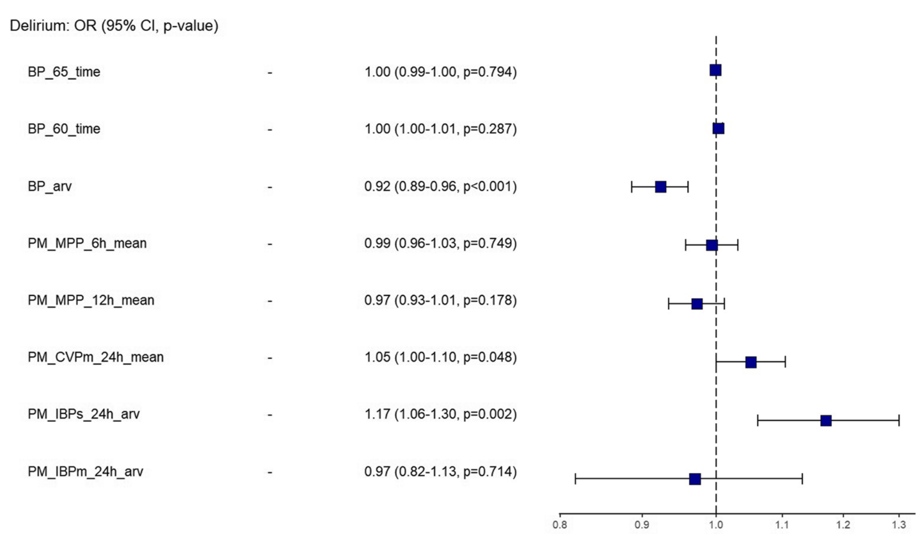

Fig. 3 Forest plot of the perioperative hemodynamic variables in predicting postoperative delirium. OR: Odds ratio, BP_65_time: time of blood pressure below 65 mmHg during operation, BP_60_time: time of blood pressure below 60 mmHg during operation, BP_arv: average real variability (ARV) of intraoperative blood pressure, PM_MPP_6h_mean: mean perfusion pressure at 6 h postoperatively, PM_MPP_12h_mean: mean perfusion pressure at 12 h postoperatively, PM_CVPm_24h_mean: mean central venous pressure at 24 h postoperatively, PM_IBPs_24h_arv: ARV of systolic blood pressure at 24 h after surgery, PM_IBPm_24h_arv: ARV of mean blood pressure at 24 h after surgery

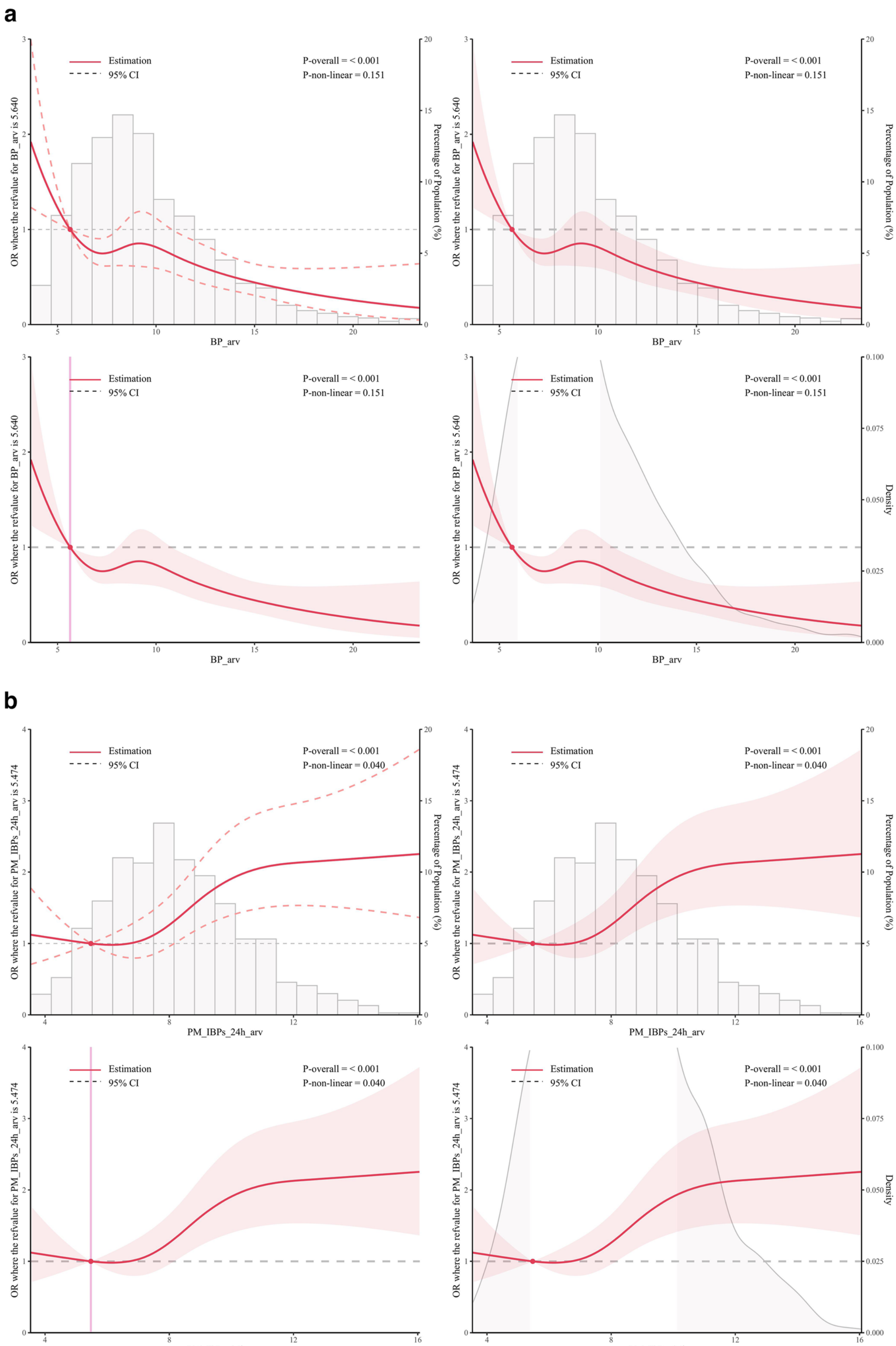

Fig. 4 Restricted cubic spline (RCS) analysis in assessing the nonlinear associations between perioperative blood pressure variability (BPV) and postoperative delirium after cardiac surgery. **A** The nonlinear associations between average real variability (ARV) of intraoperative blood pressure (BP_arv) and postoperative delirium after cardiac surgery. **B** The nonlinear associations between ARV of systolic blood pressure at 24 h after surgery (PM_IBPs_24h_arv) and postoperative delirium after cardiac surgery. OR: Odds ratio, 95% CI: 95% confidence interval

patients. A study by Hirsch et al. suggested that increased blood pressure fluctuation rather than relative hypotension was predictive of POD in the elderly patients undergoing major non-cardiac surgery [11]. Similarly, another recent study also showed that low intraoperative minimum blood pressure were risk factors for POD in the patients undergoing head and neck free flap reconstruction surgery [18]. Whereas, data on the association between perioperative ARV and POD in patients receiving cardiac surgery were insufficient. Our study first evaluated the relationship between perioperative ARV and POD in the cardiac patients and confirmed a close correlation between high postoperative ARV and the occurrence of early POD.

The influencing factors for ARV are various, including age, intraoperative blood loss, operation time, surgical stimulation, intravascular volume shifts, use of anesthetic agents, etc. [19]. In the patients receiving cardiac surgery, ARV is mostly affected by the intravascular volume status and the vasoactive drugs that used during the postoperative period. The potential mechanism for the association between ARV and POD might be as follows: Although the mean arterial pressure changes, cerebral perfusion could remain relatively stable within the range of cerebral perfusion pressure from 50 to 150 mmHg under normal physiological conditions. Whereas, the brain autonomic regulation might be compromised under anesthesia condition in those cardiac patients complicated with various co-morbidities. In this way, fluctuations in blood pressure may have a negative effect on the autoregulation function of the cerebrovascular vessels, leading to impaired cerebral perfusion and the occurrence of POD.

Perioperative hypotension used to be regarded as one important risk factor for POD in the patients underwent major surgeries [20, 21]. However, recent studies presented different opinions. A sub-analysis of the DECADE trial indicated that neither intraoperative or postoperative hypotension were associated with POD in the cardiac patients with CPB [6]. Another study found that increased blood pressure fluctuation rather than hypotension was predictive for POD in elderly patients undergoing non-cardiac surgery [11]. A latest meta-analysis suggested that a lower blood pressure target might be beneficial for the critically ill and perioperative patients compared with a higher blood pressure target [22]. Recently, a concept of "protective hemodynamics", mainly focus on minimizing damage from excessive vasoconstriction over strict blood pressure targets, was raised as a clinical strategy to maintain cardiovascular stability [23]. This concept indicated that overall optimization of hemodynamic stability rather than the solely blood pressure target was more important in reducing mortality and protecting organ functions during the perioperative period for the surgical patients. Consistent with this concept, our results also convinced that reducing the fluctuation of blood pressure might be more important than elevating blood pressure in avoiding POD for the cardiac patients during the postoperative period.

Our study has several limitations that require consideration. First of all, due to the retrospective nature of this study, the time interval for blood pressure records was every 30 min after ICU admission, which was relatively fixed. In this way, we may ignore the blood pressure fluctuation outside these time points. Secondly, we only included the cardiac patients that stayed in ICU for more than 24 h after surgery in this study, leading to the exclusion of over 50% of the cardiac patients with relatively short length of ICU stay. Whereas, the incidence of POD in our study was consistent with previous studies, showing little influence on the exclusion of those patients. Lastly, we only focused on the postoperative cognitive and mental conditions of the patients in this study, the preoperative cognitive and mental conditions were not well evaluated. However, those patients with obvious cognitive disorder and unable to communicate were excluded from this study. Further large-scale prospective clinical trial might be needed to better clarify the association between perioperative BPV and POD in the patients receiving cardiac surgery.

Conclusions

Perioperative ARV, especially postoperative high ARV exposure, was associated with POD in the patients receiving cardiac surgery. Maintaining a relatively stable blood pressure after cardiac surgery might be beneficial to avoid POD in those patients.

Abbreviations

BPV	Blood pressure variability
POD	Postoperative delirium
ICU	Intensive Care Unit
SD	Standard deviation (SD)
ARV	Average real variability
AUT_65	The area under blood pressure 65 mmHg-time curve
AUT_60	The area under blood pressure 60 mmHg-time curve
AUT_55	The area under blood pressure 55 mmHg-time curve
AUT_50	The area under blood pressure 50 mmHg-time curve
BP_65_time	Time of blood pressure < 65 mmHg
BP_60_time	Time of blood pressure < 60 mmHg
BP_55_time	Time of blood pressure < 55 mmHg
BP_50_time	Time of blood pressure < 50 mmHg
TWA_BP_65	Time-weighted average threshold value for blood pressure < 65 mmHg
TWA_BP_60	Time-weighted average threshold value for blood pressure < 60 mmHg
TWA_BP_55	Time-weighted average threshold value for blood pressure < 55 mmHg
TWA_BP_50	Time-weighted average threshold value for blood pressure < 50 mmHg
HR	Heart Rate
IBPs	Systolic blood pressure
IBPd	Diastolic blood pressure
IBPm	Mean blood pressure
CVP	Central venous pressure

BP_mean	Mean blood pressure
BP_arv	Average real variability of blood pressure
CPB	Cardiopulmonary bypass
NYHA	New York Heart Association
MAP	Mean arterial pressure
CVICU	Cardiovascular Intensive Care Unit
BMI	Body mass index
APACHE II	Acute Physiology and Chronic Health Evaluation II score
euroSCORE	European System for Cardiac Operative Risk Evaluation
CAD	Coronary artery disease
CRF	Chronic renal failure
AF	Atrial fibrillation
COPD	Chronic obstructive pulmonary disease
EHRs	Electronic health records
BP	Blood pressure
SpO_2	Pulse oxygen saturation
IABP	Intra-aortic balloon pump
ECMO	Extracorporeal membrane oxygenation
AKI	Acute kidney injury
RRT	Renal replacement therapy
CAM-ICU	Confusion assessment method for Intensive Care Unit
RASS	Richmond Agitation-Sedation scale
IQR	Interquartile range
LASSO	Least absolute shrinkage and selection operator
RCS	Restricted cubic spline
CABG	Coronary artery bypass grafting
AAAD	Acute Stanford Type A aortic dissection
MPP	Mean perfusion pressure

Supplementary Information

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Supplementary Material 1.

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Not applicable.

Authors' contributions
XS and HT contributed to design, data acquisition, statistical analysis and drafted the manuscript. WXC and JKS contributed to data acquisition, data analysis and presentation. RHJ and WHZ contributed to data acquisition and data analysis. LH and CZ contributed to study control, study design and manuscript drafting. CZ contributed to manuscript drafting and revision. XS and HT contributed equally to the paper. All authors have read and approved the final manuscript.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Nanjing First Hospital, Nanjing Medical University (KY20220518-01-KS-01) with a waiver of the requirement for informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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