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ORIGINAL ARTICLE

Cognitive Functions after Open Heart Surgeries: Comparison between Inhalational and Total Intravenous Anesthesia

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ABSTRACT

Background: Postoperative cognitive dysfunction (POCD) is a frequent significant complication post-cardiac surgery. Quoted incidences are dependent on variable factors: timing of measurements, the type of surgery, the exact assessment used, and its sensitivity. The role of anesthetic agent in POCD is still uncertain.

Objective: to study the cognitive functions after isoflurane- compared with propofol-based anesthesia for open heart surgeries.

Patients and Methods: In this prospective study, 260 patients undergoing elective open heart surgery were included and allocated into 2 equal groups: isoflurane-based anesthesia and propofol-based anesthesia. POCD was defined as deterioration ≥ 20% from baseline in at least 2 of the neurocognitive tests. Battery of seven neurocognitive tests was applied to assess the patients before and 3 to 7 days after surgery.

Results: The incidence of POCD in our study was 43.6%, with no significant difference between both isoflurane group (38.4%) and propofol group (48.8%), P=0.097. POCD had a significant association with: age, body mass index, educationa level, hypertension, diabetes, type of surgery, ejection fraction, time of operation, cardiopulmonary bypass (CPB) time, aortic cross clamp (ACC) time and intraoperative complication. However, only low educational level (P=0.013) and ACC time (P<0.001) were the independent risk factors for POCD.

Conlusion: There is no significant difference between isoflurane- or propofol-based anesthesia on POCD incidence. Low education level and ACC time are independent risk factors for POCD.

Keywords: Cognitive dysfunction, Isoflurane, Propofol, Open heart surgery

INTRODUCTION

One of the most important causes of post-cardiac surgery morbidity and mortality is the neurological damage. Stroke and Postoperative cognitive dysfunction (POCD) are the two most significant neurological outcomes after cardiac surgery[(1)]. There is no exact pathophysiology that can explain cognitive dysfunction after cardiac surgery, Mostly it seems to be multifactorial with the main 3 sides of the procedure: surgery, patient and anesthesia[(2)]. Anesthesia has a dual action: neuroprotective and neurotoxic with difficulty to evaluate its impact on POCD[(3)]. The main predictors of anesthesia to cause POCD are type of anesthesia, anesthetic dose, route of delivery and time of observation[(4)]. Small studies documented that inhalational anesthesia in cardiac surgery could have a better cognitive outcome than total intravenous anesthesia which is different in non-cardiac surgery[(5)].The role of anesthetic agent in POCD is still uncertain. So, more clinical trials are needed to know if there are beneficial effects.

Several cognitive parameters may be affected such as attention, memory, learning, visual, motor skills, and practical function.

Also behavioral change is included. So, variable neuropsychological tests are used to confirm POCD clinically several weeks after surgery and compared with preoperative tests[(6)].

The aim of this study was to study the cognitive functions after isoflurane- compared with propofol-based anesthesia for open heart surgeries. The secondary aim of this study was detecting the incidences of cognitive dysfunction, detecting the most common neurological disorders and detecting the potential risk factors for POCD after open heart surgeries in Zagazig university hospitals.

PATIENTS AND METHODS

This prospective randomized study was approved by Institutional Review Board (IRB), carried out at Zagazig university hospitals on 260 patients.

Inclusion criteria included; aged from 21-60 years old, of both sexes, body mass index (BMI) from 18.5-30 kg m^{-2}, ejection fraction (EF) ≥ 50%, normal hepatic and renal functions, undergoing elective open heart surgery.

Exclusion criteria included; preexisting neuropsychiatric disorders, emergency surgery, illiterate patients, allergy to study medication, mini-mental state examination (MMSE) score ≤ 23, patients with vision or hearing problems, patients with alcohol or drug addiction.

Withdrawal criteria included; delayed patient's recovery >24 hours, early postoperative mortality, postoperative delirium and lost to follow up.

Randomization was applied by computer generated number tables. Patients were randomly allocated into 2 equal groups, but 10 patients couldn't be analysed for variable reasons. The final number of patients were analysed was 250 (125 patients in ***propofol group*** and 125 patients in ***isoflurane group***) **(Fig 1)**.

Written informed consent was obtained from all participants. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Patients' evaluation for cognitive function was applied twice; one 24 hour preoperative in a quiet room in the ward and another postoperative after patient's discharge from ICU and before hospital discharge (3rd to 7th day). All patients were informed well about the neurocognitive tests. The neuropsychological evaluation took about 45 minutes for each patient. Also, demographic data and surgical data were recorded for both groups **(Table 1).**

Seven neurocognitive tests were used to evaluate all patients included:

(1) Mini-Mental State Examination (MMSE): as a rapid global cognitive assessment. The endpoint of the test was to get the greater score from the total 30 points score.

(2, 3) The Rey Auditory Verbal Learning Test (RAVLT): assessed the episodic memory. The endpoint of the test was the sum of A_{1-5} trials (immediate recall) and A_7 trial (delayed recall).

(4) The Trail Making Test (TMT): assessed information processing speed and attention. The endpoint of the test was the time of completion.

(5, 6) Digit Span Test (DST) (forward and backward): which assessed attention (forward) and working memory (backward). The endpoint of the test was the sum of number correct.

(7) Benton Visual Retention Test (BVRT): assessed immediate visual memory. The endpoint of the test was the number of correct figures.

The analytic criteria which defined the patients' postoperative cognitive dysfunction were "the percentage decline". The patient; who showed a deterioration ≥ 20% from baseline in at least 2 of the neurocognitive tests, was considered POCD[(7)].

All patients received 0.025-0.05 mg/kg midazolam i.v as a premedication, then in the operating room, standard monitors including non-invasive blood pressure (NIBP), digital pulse oximetry and 5-lead electrocardiogram were connected to the patients, arterial cannula for invasive blood pressure monitoring. Capnogram and temperature probes were applied to each patient and central venous catheter was inserted after induction of anesthesia.

General anesthesia was induced by 5-10 µg/kg fentanyl, 1-2 mg/kg thiopentone and 0.6-1.2 mg/kg rocuronium were injected i.v to facilitate tracheal intubation. Patients were connected to the operating room ventilator immediately after intubation with F^IO^2=1, tidal volume=8-10ml/kg and respiratory rate=12-16 breath/min to maintain $Etco_2$=30-35mmHg. Anesthesia was maintained with opioid (fentanyl 3–5 µg/kg/h in repeated boluses), neuromuscular blocking agent (rocuronium 10 µg/kg/min continuous infusion), and either isoflurane or propofol.

Before cardiopulmonary bypass (CPB), all patients received 4-5 mg/kg heparin to get an activated clotting time (ACT) ≥ 480 sec. After CPB initiation, mild systemic hypothermia (33-35 ^{o}C) was maintained. CPB flow target was 2.2-2.5 L/min/m^2 and the MAP was maintained between 45-70 mmHg. Anesthesia was maintained during CPB by rocuronium (50mg), fentanyl (100µg) and midazolam (5mg) all as repeated boluses. Gradual rewarming was allowed without exceeding 37^{o}C. After aortic declamping, inotropic support was started regarding the cardiac performance (contractility and heart rate) and hemodynamics. After weaning from CPB, protamine was given by 6 mg/kg or till reaching the patient's basal ACT. After surgery, patients were sedated by propofol till recovery in the ICU.

Anesthetic regimen for isoflurane group (Group I):

After induction of anesthesia, patients received isoflurane 0.5-2 minimum alveolar concentration (MAC) till starting CPB; it was stopped. After aortic declamping, isoflurane was continued till the end of the operation.

Anesthesia regimen for propofol group (Group T):

After induction of anesthesia, patients received propofol 3-5 mg/kg/h till the end of the operation then the rate was reduced to 2 mg/kg/h during ICU transfer and till recovery.

Study outcome measures:

- Primary outcome measure: detect the incidence of POCD after isoflurane-compared with propofol-based anesthesia.
- Secondary outcome measures: detect the incidence of POCD, detecting the most common postoperative neurological disorders and detecting the potential risk factors for POCD.

Sample size:

Assuming that the percentage of cognitive dysfunction after propofol versus inhalational anesthesia is 67.5% vs 49.4% respectively[(5)]. Using Epi info version 6 with power 80% and C.I 95%, the total sample size is 252 patients (126 in each group).

Statistical Analysis:

The data were analyzed by IBM SPSS advanced statistics (Statistical Package for Social Sciences), version 22 (SPSS Inc., Chicago, IL). Numerical data were described as mean and standard deviation or median and range as appropriate. Comparisons between categorical variable were performed using chi square test or fissure exact test when assumption of chi square was not fulfilled. Mann Whitney test was used to compare non-normally distributed numerical variable and detect significant differences in demographic, operative data and cognitive function between isoflurane and propofol patients and also between POCD and non-POCD patients. The probability value (p-value) ≤ ***0.05*** was considered *statistically significant.*

RESULTS

The incidence of POCD before hospital discharge showed no significant difference between both isoflurane group (48/125(38.4%) and propofol group (61/125(48.8%), P=0.097 **(Table 1)**. The demographic and surgical variables had been analysed by univariate analysis to detect the potential risk factors for POCD **(Table 2).** From 250 patients, 109 (43.6%) had matched the POCD diagnostic criteria. POCD patients were significantly older than non-POCD (P<0.001). Higher BMI (27.16 kg/m^2) was significant and correlated with POCD patients (P=0.019). Patients with low educational level had lower neurocognitive tests' scores with POCD (P<0.001). **Figure 2** shows that participation of low educational level population was more than high education with higher incidence of POCD between low education (50.26%) than high education

(23.8%). Also in this study, there was a significant relationship between POCD and medical history of hypertension (P=0.001). Another significant relationship with DM (P=0.001).Type of surgery showed significant differences with POCD (P=0.001) especially combined surgeries which showed the highest incidence of POCD (100%) and the lowest incidence was in valvular surgeries (34.89%) **(Fig 3).** Ejection fraction also, has a significant relationship (P=0.029), longer operative time (P<0.001), CPB time (P<0.001), aortic cross clamping time (P<0.001) and intraoperative complications (including hypokalemia, hyperkalemia and the need of intra-aortic balloon insertion) (P=0.023).

All factors; which were statistically significant for POCD association after univariate analysis, were screened secondarily by multivariate logistic regression analysis including age, BMI, educational level, medical history of DM or hypertension, type of surgery, ejection fraction, operative, CPB, cross clamping time and intraoperative complications. Only low educational level (P=0.013) and ACC time (P<0.001) were the independent risk factors for early POCD **(Table 3)**.

Table 1: Patient's characteristics and surgical data between both groups:

		Isoflurane		**Propofol**		**P value**
		N=125	%	N=125	%	
Age/year (Mean±SD)		50.09±9.90		47.94±10.54		0.107 (NS)
Sex	Male	70	56.0%	74	59.2%	0.610 (NS)
	Female	55	44.0%	51	40.8%	
Body mass index(Kg/m^2) (Mean±SD)		26.70±2.75		26.76±2.80		0.852 (NS)
Education Level	Low	89	71.2%	98	78.4%	0.190 (NS)
	High	36	28.8%	27	21.6%	
Hypertension	No	73	58.4%	71	56.8%	0.702 (NS)
	Yes	52	41.6%	54	43.2%	
Diabetes	No	100	80.0%	102	81.6%	0.633 (NS)
	Yes	25	20.0%	23	18.4%	
Atrial fibrillation	No	104	83.2%	102	81.6%	0.740 (NS)
	Yes	21	16.8%	23	18.4%	
Type of surgery	CABG	49	39.2%	50	39.2%	0.844 (NS)
	Valvular	74	58.2%	75	60.0%	
	Combined	2	1.6%	1	0.8%	
Ejection fraction (%) (Mean±SD)		61.48±7.78		62.63±7.56		0.181 (NS)
Operative time/min (Mean±SD)		301.84±84.96		309.52±74.89		0.384 (NS)
Cardiopulmonary bypass time/min (Mean±SD)		115.80±41.56		111.20±32.80		0.266 (NS)
Aortic cross clamping time/min (Mean±SD)		87.60±33.99		86.12±29.75		0.394 (NS)
Intraoperative complications	No	111	88.8%	113	90.4%	0.746(NS)
	Hypokalemia	9	7.2%	10	8.0%	
	Hyperkalemia	2	1.6%	0	0.0%	
	Intra-aortic balloon	3	2.4%	2	1.6%	
Post-Operative Cognitive Dysfunction(POCD)	No POCD	77	61.6%	64	51.2%	0.097 (NS)
	POCD	48	38.4%	61	48.8%	

(CABG) Coronary Artery Bypass Grafting. (NS) not statistically significant. P value set significant ≤0.05, Chi square and Mann Whitney tests were used

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Table 2: Relation between patient's characteristics and surgical data and Postoperative Cognitive Dysfunction (POCD):

		No POCD		**POCD**		**P value**
		N= 141	%	N= 109	%	
Age/year (Mean±SD)		46.58±10.70		52.17±8.75		<0.001(S)
Sex	Male	79	56.0%	65	59.6%	0.567(NS)
	Female	62	44.0%	44	40.4%	
Body mass index(Kg/m^2) (Mean±SD)		26.40±2.84		27.16±2.63		0.019(S)
Education Level	Low	93	66.0%	94	86.2%	<0.001(S)
	High	48	34.0%	15	13.8%	
Hypertension (n=106)		47	33.3%	59	54.1%	0.001(S)
Diabetes (n=48)		17	12.1%	31	28.4%	0.001(S)
Atrial fibrillation (n=17)		3	21.3%	14	12.8%	0.083(NS)
Type of surgery	CABG	44	31.2%	54	49.5%	0.001(S)
	Valvular	97	68.8%	52	47.7%	
	Combined	0	0.0%	3	2.8%	
Ejection fraction (%) (Mean±SD)		62.95±7.37		60.90±7.95		0.029(S)
Operative time/min (Mean±SD)		284.61±75.10		332.94±78.24		<0.001(S)
Cardiopulmonary bypass time/min (Mean±SD)		101.35±34.61		129.22±35.15		<0.001(S)
Aortic cross clamping time/min (Mean±SD)		76.63±29.20		100.09±29.79		<0.001(S)
Intraoperative complication	No	133	94.3%	91	83.5%	0.023(S)
	Hypokalemia	6	4.3%	13	11.9%	
	Hyperkalemia	1	0.7%	1	0.9%	
	Intra-aortic balloon	1	0.7%	4	3.7%	

(CABG) Coronary Artery Bypass Grafting. (S) Statistically significant. (NS) not statistically significant. P value set significant ≤0.05, Chi square and Mann Whitney tests were used

Table 3: Logistic regression analysis for factors associated with POCD:

	B	S.E.	P value	Odds ratio	95% C.I. for odds ratio	
					Lower	Upper
Aortic cross clamping time/min	0.024	0.005	<0.001	1.024	1.015	1.033
Education Level	0.872	.350	0.013	2.392	1.204	4.749

By entering all significant variables in table 2 only Aortic cross clamping time/min and education level were significant. (B) Beta Coefficient, (SE) Standard Error, (C.I.) Confidence Interval

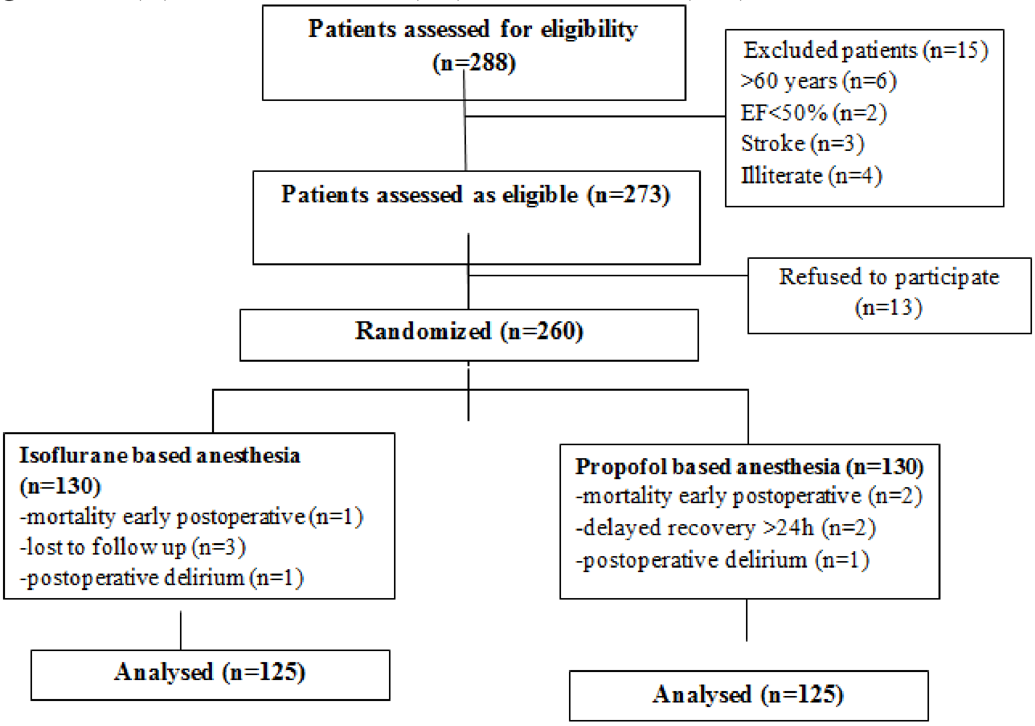

Figure 1. Study population flow chart

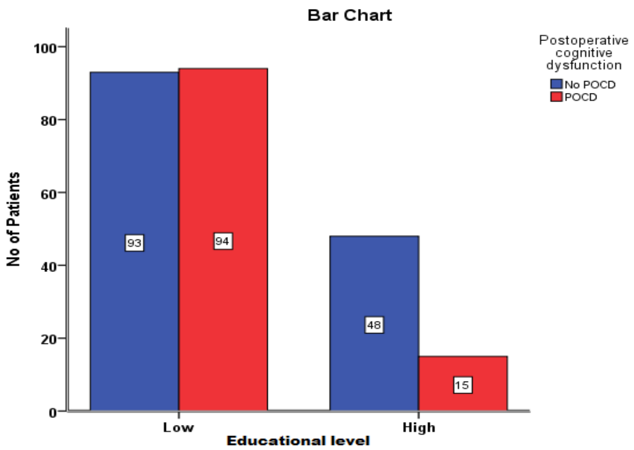

Figure 2. Educational level between Postoperative cognitive dysfunction groups

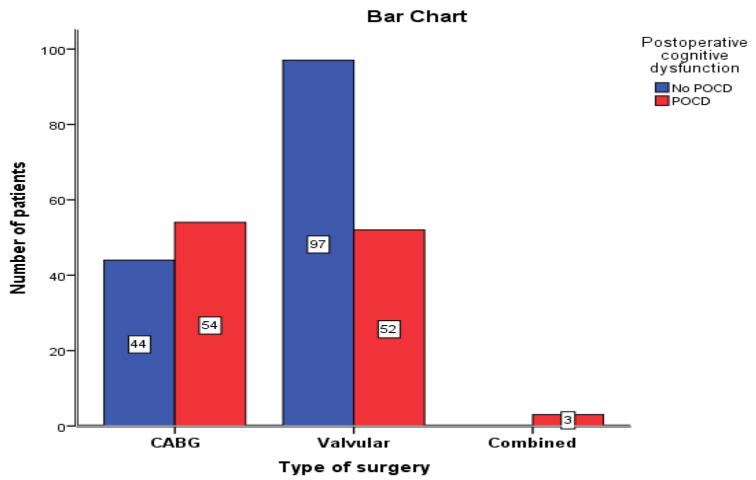

Figure 3. Types of surgery between Postoperative cognitive dysfunction groups

DISCUSSION

In this study, the primary objective was to identify the most effective type of anesthesia associated with lower incidence of POCD, but the incidence of early POCD following open heart surgeries wasn't significantly affected by the type of anesthesia (either isoflurane or propofol). These results were comparable to previous studies using different types of anesthesia. In a small prospective study, no cerebral protective benefits were found from using propofol rather than isoflurane for CABG candidates [(8)]. By another retrospective study, inhalational anesthesia (sevoflurane) didn't reduce POCD [(9)]. Also other previous large study on patients underwent different types of surgeries; the cardiac surgery group (all CABG) showed the same negative results (using TIVA only) [(10)]. In other types of surgery the same findings were observed, as Münte et al. found that no difference in postoperative cognitive outcome between isoflurane and propofol based anesthesia in patients underwent interventional neuroradiology procedures [(11)]. However, there are other studies had showed that inhalational anesthesia regimen had better postoperative cognitive outcome [(5, 12-14)]. In these studies, the neuroprotective effect of volatile anesthetics can't be tested, because they were used in combination with analgesics and sedatives and propofol was used for all patients in ICU for sedation.

Additionally, the secondary objective in this study was to detect the most common neurological disorders after open heart surgeries in Zagazig university hospitals and calculate their incidences. Variable types of neurological damage had been occurred, especially stroke, delirium and POCD **(Fig 1)**. The most frequent complication was POCD by general incidence 43.6%. That was comparable to the results of previous studies (39.8%, 40.7% and 44.5%) which also applied on patients underwent cardiac surgeries [(15-17)]. Other previous studies showed higher incidence of POCD but with different demographic and surgical input data rather our study (table 1). Royse et al. reported early POCD with general incidence 58% and including elderly people >70 years old, obese patients with BMI >30, and patients underwent coronary artery bypass surgery only [(5)]. Another previous study with higher POCD incidence of 55%, had included patients with higher mean of age, patients with carotid artery disease and hyperlipidemia and finally most of the population study underwent CABG surgery. All these factors also are more risky for POCD occurrence [(18)]. On the other hand, there were previous studies with lower POCD incidence like the Chinese study with 33% general incidence of early POCD, lower mean of age, lower BMI, shorter mean of CPB and ACC period and including patients underwent non-coronary bypass surgery only [(19)]. The incidences of delirium, stroke and mortality in this study were 0.7%, 0.7% and 1.15% respectively.

The third objective to the current study was to detect the risk factors for POCD rather than the type of anesthesia. Age in our study had a significant relationship with POCD (P<0.001) and that was similar to previous studies which reported worse postoperative cognitive function with elderly population [17-20]. Patients with higher BMI were significantly associated with POCD (P=0.019). A contrast results were found in other studies, in which there was no relationship between BMI and POCD [16, 18, 19]. A significant association between patients with medical history of hypertension and POCD (P=0.001), but in a recent large meta-analysis including cardiac surgeries, there was no association between hypertension and POCD (P=0.82) [21]. Only two studies from this meta-analysis detected hypertension as predictor for POCD [22, 23]. Medical history of DM has showed a significant association with POCD incidence (P=0.001). The same significant association was found in previous studies between both types of DM and either early POCD [12] or late POCD [24]. Type of surgery especially combined surgery (valvular and CABG) also has a significant association with POCD in this study (P=0.001). A recent study reported similar results between POCD and CABG (P=0.035) [18]. Ejection fraction results were statistically significant with POCD (P=0.029). However, the EF mean of non-POCD (62.95%) was so near to POCD (60.90%). Operation time was significantly associated with POCD (P<0.001). This result was the same as the Chinese study[19]. Most cases passed surgery without any significant intraoperative complications, but complicated cases with hypokalemia, hyperkalemia and the need for intra-aortic balloon insertion were significantly associated with POCD (P=0.023). Many studies reported a significant association between POCD and both CPB time and ACC time [16, 19, 25]. Although in the current study both have a significant association with POCD (P<0.001 for both), but only ACC time beside educational level are the independent predictors for early POCD according to the logistic regression analysis. Many studies reported higher incidence of POCD between low educational level population, but some of them considered the results as non-statistically significant [16, 17], and the other reported low educational level as independent risk factor for POCD [12, 26].

Limitations of the current study were: First, the types of anesthesia (either isoflurane or propofol) haven't been tested separately from other intra- or postoperative medications (sedatives and analgesics) which may have their own impact on the patient's cognitive function. Second, this study evaluated the early POCD till hospital discharge only, with lack of evaluating long-term cognitive outcome. Third, this study was a single-station study. Fourth, there was a large variability in this study population demographic and surgical data, so further studies better be applied on a more homogenous population with analogous preoperative status and surgical trauma.

CONCLUSION

The incidence of early POCD in Zagazig university hospitals is 43.6%. However, the type of anesthesia; neither isoflurane nor propofol, affected the incidence of POCD. Also, gender and AF have no significant association with POCD in this study. By logistic regression analysis, only lower educational level and longer ACC time are the potential risk factors for early POCD. However, advanced age, higher BMI, low educational level, hypertension, DM, type of surgery, EF, intraoperative complications, longer operative time, CPB time and ACC time, all show significant association with POCD incidence.

Conflicts of interest
There are no conflicts of interest
Financial Disclosures. No

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