ORIGINAL CLINICAL RESEARCH REPORT

Volatile Versus Total Intravenous Anesthesia on Postoperative Delirium in Adult Patients Undergoing Cardiac Valve Surgery: A Randomized Clinical Trial

Jia-Li Jiang, MD,* Lu Zhang, MD,* Lei-Lei He, MD,† Hong Yu, MD,* Xue-Fei Li, MD,* Shun-Hui Dai, BSN,* and Hai Yu, MD, PhD*

BACKGROUND: The effect of anesthesia regimens on postoperative delirium after on-pump cardiac valve surgery is yet undetermined. This study aimed to evaluate the effect of volatile anesthesia compared with propofol-based total intravenous anesthesia (TIVA) on the occurrence of delirium after on-pump cardiac valve surgery.

METHODS: This randomized clinical trial was conducted at a university academic hospital in China, from February 2019 to January 2021. Patients scheduled for on-pump cardiac valve surgery or combined valve with coronary artery bypass grafting (CABG) surgeries were randomly assigned to receive anesthesia maintenance with either a volatile anesthetic (sevoflurane or desflurane) or propofol-based TIVA. The primary outcome was the incidence of delirium during the first 7 days after surgery, assessed using the confusion assessment method for the intensive care unit (ICU). The secondary outcomes included duration of delirium, subtypes of delirium, 30-day mortality, pain score, major morbidity (including cerebral infarction, respiratory failure, and pneumonia), duration of mechanical ventilation, and lengths of ICU and hospital stay. The statistical analysis of the primary outcome variable was by Pearson's χ^2 test.

RESULTS: Among the 684 patients analyzed (mean age, 53.8 years; 381 [55.7%] women), 676 were assessed for the primary outcome. Postoperative delirium occurred in 63 of 337 (18.7%) patients receiving volatile anesthesia versus 76 of 339 (22.4%) patients receiving propofol-based TIVA (relative risk, 0.80; 95% confidence interval [CI], 0.55–1.16; $P = .231$). There were no significant differences between the groups in any of the secondary outcomes.

CONCLUSIONS: Among patients undergoing on-pump cardiac valve surgery, anesthesia maintenance with a volatile agent did not result in significantly fewer occurrences of postoperative delirium than propofol-based TIVA. (Anesth Analg 2022;00:00–00)

KEY POINTS

- **Question:** Dose volatile anesthesia reduces the occurrence of delirium after on-pump cardiac valve surgery when compared with intravenous anesthesia?
- **Findings:** Compared with propofol-based intravenous anesthesia, anesthesia maintenance with a volatile agent did not result in fewer cases of postoperative delirium in patients undergoing on-pump cardiac valve surgery.
- **Meaning:** Our data did not provide sufficient evidence that the choice of volatile or intravenous anesthesia affects the risk of developing delirium after on-pump cardiac valve surgery.

GLOSSARY

ASA = American Society of Anesthesiologists; **CABG** = coronary artery bypass grafting; **CAM** = confusion assessment method; **CI** = confidence interval; **CONSORT** = Consolidated Standards of Reporting Trials; **COPD** = chronic obstructive pulmonary disease; **CPB** = cardiopulmonary bypass; **ERAS** = Enhanced Recovery after Surgery; **EuroSCORE** = European System for Cardiac Operative Risk Evaluation; **ICU** = intensive care unit; **IQR** = interquartile range; **ITT** = intention to treat; **MAC** = minimal alveolar concentration; **NRS** = numerical rating scale; **NYHA** = New York Heart Association; **POD** = postoperative delirium; **PP** = per protocol;

From the *Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, China; and †Department of Anesthesiology, Sichuan Jinxin Women and Children's Hospital, Chengdu, Sichuan, China.

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J.-L. Jiang and L. Zhang contributed equally to the work.

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Address correspondence to Hai Yu, MD, PhD, Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China. Address e-mail to yuhai@scu.edu.cn.

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RASS = Richmond Agitation-Sedation Scale; **RBC** = red blood cell; **RHD** = rheumatic valve disease; **RR** = relative risk; **SD** = standard deviation; **TIVA** = total intravenous anesthesia; **VA** = volatile anesthesia

In China alone, more than 180,000 people undergo cardiac surgery with cardiopulmonary bypass (CPB) annually. Among adult cardiac surgery patients, valve surgery is the most common procedure, which represents an important patient population that merits investigation and consideration.[1] Despite advances in surgical techniques, anesthetic management, and perioperative care, morbidity related to cardiac surgery is still high.[2]

Postoperative delirium (POD) is a frequently observed complication after cardiac surgery with an incidence of 26% to 52%,[3] characterized by disturbances of consciousness, attention, cognition, or perception.[4] Patients with valve replacement appear at higher risk of POD than patients subjected to coronary artery bypass grafting (CABG) alone.[5] Notably, patients who experience delirium have an impaired recovery, prolonged hospital stay, functional and cognitive decline, a higher incidence of morbidity and mortality, and increased costs.[6] Interventions in different surgical settings (both cardiac and noncardiac surgeries) have shown that a reduction in delirium can result in improved clinical outcomes and lower costs.[7–9] With the rapid evolution of perioperative medicine and improved insights into delirium and its determinants, preventive and therapeutic strategies are highly needed.

Although general anesthesia is the standard anesthetic technique in cardiac surgery, there is varied evidence regarding the anesthesia regimens and postoperative outcomes. Several meta-analyses and studies evaluated the impact of anesthesia regimens on mortality and morbidity related to cardiac surgery and reported mixed results.[10–14] However, these studies did not report the effect on delirium. Even so, a meta-analysis of 13 randomized trials in patients undergoing cardiac surgery revealed that volatile anesthesia (VA) provided better cerebral protection than total intravenous anesthesia (TIVA).[15] Additionally, limited evidence suggests that VA can reduce the levels of biochemical markers of brain injury and the incidence of postoperative neurocognitive dysfunction in patients undergoing cardiac surgery.[16] However, a recent systematic review did not find that volatile anesthetics might reduce the occurrence of delirium after cardiac surgery.[17] Unfortunately, all of the published studies have significant limitations that impeded definite conclusions. The differences between the 2 anesthesia regimens with respect to the risk of acute brain dysfunction or cognitive impairment after cardiac valve surgery are unclear.

Accordingly, this randomized clinical trial was conducted to evaluate the effect of VA compared with propofol-based TIVA on the occurrence of delirium after on-pump cardiac valve surgery. It was hypothesized that VA as a maintenance type of anesthesia would reduce the incidence of delirium within the first 7 postoperative days.

METHODS

Study Design

This was a single-center, pragmatic, randomized controlled trial with 2 parallel arms. This trial was approved by the Ethical Committee of the West China Hospital of Sichuan University (Ethical Committee No. 2018 [561]) and registered at the Chinese Clinical Trial Registry (ChiCTR1900021355, principal investigator: Hai Yu, date of registration: February 16, 2019. http://www.chictr.org.cn/showproj.aspx?proj=36071.) before the first patient was enrolled. The research was completed according to the standards established in the Declaration of Helsinki,[18] and written informed consent was obtained from all participants. This report followed the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting parallel group randomized trials.[19]

Participants

Adult patients (ages 18 years or older) undergoing elective on-pump cardiac valve surgery or combined valve with CABG surgeries were enrolled. The exclusion criteria were unable to communicate effectively due to visual, auditory, or language impairments; American Society of Anesthesiologists classification IV or above; previous history of neurosurgery or brain trauma, epilepsy, Parkinson's disease, dementia, schizophrenia, depression, or alcoholism; previous history of using benzodiazepine, major tranquilizers, or steroids; severe hepatic insufficiency (Child-Pugh classification C); renal failure requiring dialysis; and suspected of being allergic to study drugs or malignant hyperthermia.

Randomization and Blinding

After written informed consent, patients were randomly allocated (1:1) according to the random allocation list generated by SPSS 22.0 to either the VA group or TIVA group. The randomization codes remained in sealed sequentially numbered opaque envelopes and were sent to a research coordinator of the research team the day before the surgery. The coordinator communicated the group assignment to

the anesthesiologist who was in charge of the patient care but was not involved in the study. One investigator was responsible for patient screening, enrollment, and preoperative neurological assessments. Outcome assessors were responsible for postoperative follow-up. Patients, surgeons, intensive care physicians, outcome assessors, and statisticians were blinded to the group assignment.

Interventions

Patients in the VA group received sevoflurane or desflurane at a minimum end-tidal concentration of 0.5 to 2 minimal alveolar concentration (MAC) during maintenance of anesthesia, including CPB. Patients in the TIVA group received propofol at an infusion rate of 3 to 8 $mg \cdot kg^{-1} \cdot h^{-1}$ throughout the entire procedure. Sevoflurane, desflurane, or propofol concentration, allowed to exceed the specified rate in a short period, was titrated to achieve a target bispectral index value of 40 to 60.

Perioperative Management

General anesthesia was induced with midazolam, sufentanil, and cisatracurium, combined with etomidate if necessary. In addition to volatile anesthetics or propofol, anesthesia was maintained with a continuous infusion of remifentanil and intermittent sufentanil and cisatracurium. Patients received standard institutional monitoring, including electrocardiogram, temperature, invasive blood pressure, central venous pressure, and transesophageal echocardiography. Pump equipment included a roller pump, membrane oxygenator (Medtronic), and tubing system. Nonpulsatile flow was maintained between 2.2 and 2.4 $L \cdot min^{-1} \cdot (m^2)^{-1}$. During CPB, body temperature was maintained at 32 °C to 34 °C, and the mean arterial pressure was maintained between 50 and 80 mm Hg. After bypass, anticoagulation was reversed with protamine.

After surgery, patients were transferred to the intensive care unit (ICU) for additional care. Postoperative care was left at the discretion of the ICU intensivist. Extubation was considered when patients were normothermic, spontaneously breathing, conscious, and hemodynamically stable. Patients were sedated with a propofol or dexmedetomidine infusion until they met extubation criteria in the ICU.

Outcome Measures

Primary Outcome. The primary outcome was the incidence of delirium within the first 7 postoperative days. The delirium was assessed with the confusion assessment method for the ICU (CAM-ICU) once a day (15:00–17:00) during postoperative days 1 to 7. If discharged within 7 days after surgery, the last assessment was performed on the day of discharge. The CAM-ICU is a specific assessment tool for patients in ICU and has high sensitivity and specificity.[20] The CAM-ICU defines delirium by 4 features: (1) acute onset of changes or fluctuations in the course of mental status; (2) inattention; (3) disorganized thinking; and (4) an altered level of consciousness. If the patients show both features of 1 and 2 and also an additional feature of 3 or 4, he or she is suggested to be in delirium.[21] The assessment process is divided into 2 steps. The first step: assess the level of consciousness using the Richmond Agitation-Sedation Scale (RASS); the second step: assess the content of consciousness using CAM-ICU. The delirium was assessed by the CAM-ICU only when the RASS score is >–4.

Secondary Outcomes. The secondary outcomes included duration of delirium, subtypes of delirium, 30-day all-cause mortality, pain score within the first 3 days after surgery, major morbidity (including cerebral infarction, respiratory failure, and pneumonia), duration of mechanical ventilation, and lengths of ICU and hospital stay. The subtype of delirium can be determined using the RASS score: hypoactive type, RASS score <0; hyperactive type, RASS score >0; and mixed type, the hypoactive and hyperactive types occur alternately.[22] Pain intensity was assessed using a numerical rating scale (NRS).

Statistical Analysis

All analyses were conducted according to the intention-to-treat (ITT) principle. Per-protocol (PP) analysis was also performed for the outcomes. A descriptive analysis was applied to describe the baseline characteristics. Standardized differences were presented, and variables with standardized differences >1.96 $\mathrm{sqrt}[(1/n_1) + (1/n_2)]$ were considered imbalanced.[23] In this study, standardized differences ≥0.150 were considered imbalanced. The frequency and percentage of missing values for each variable were collected, analyzed, and reported as necessary. Normality of distribution was assessed with the Kolmogorov-Smirnov test. Continuous variables were presented as mean (standard deviation [SD]) or median (interquartile range) according to the distribution. Independent Student *t* or Mann-Whitney *U* test was applied for between-group comparisons of continuous variables as appropriate. Categorical data were presented as number with percentage. Pearson's χ^2 test was used for comparison between groups. Fisher exact test was used only when the expected counts were <5 for at least 25% of the cells. Time-to-event results were analyzed using the Kaplan-Meier survival analysis, with the difference between groups tested by the log-rank test. The heterogeneity of the treatment effect on the primary outcome was assessed in prespecified subgroups by

adding an interaction term to a logistic regression model. The interaction between treatment and each of the variables, including sex, age, education level, history of stroke, and baseline cognition, was tested, respectively. Sensitivity analyses included adding patients who were comatose at all in-person assessments to the delirium group because some argued that coma was a severe form of acute brain injury.[24] The outcomes were expressed as relative risks (RRs) with 95% confidence intervals (CIs). All analyses were performed using SPSS Statistics version 22.0 for Windows (SPSS Inc). A 2-sided *P* value <.05 was considered statistically significant with exact *P* values given unless *P* <.001.

The present study was powered to detect the difference in delirium incidence within the first 7 days after surgery between the VA group and TIVA group. Based on our clinical observation and published delirium studies in the scientific literature,[25–27] the incidence of delirium after cardiac surgery under propofol-based TIVA was assumed to be 25%. The calculated sample size was 332 patients in each group with an 80% power (β = 0.2) and a significant level (α) of 0.05 to show a 35% relative reduction (an 8.75% absolute decrease) in the primary outcome between the 2 arms. A previous study demonstrated that the reduction in delirium exceeding at least one-third of the baseline rate was considered clinically relevant.[28]

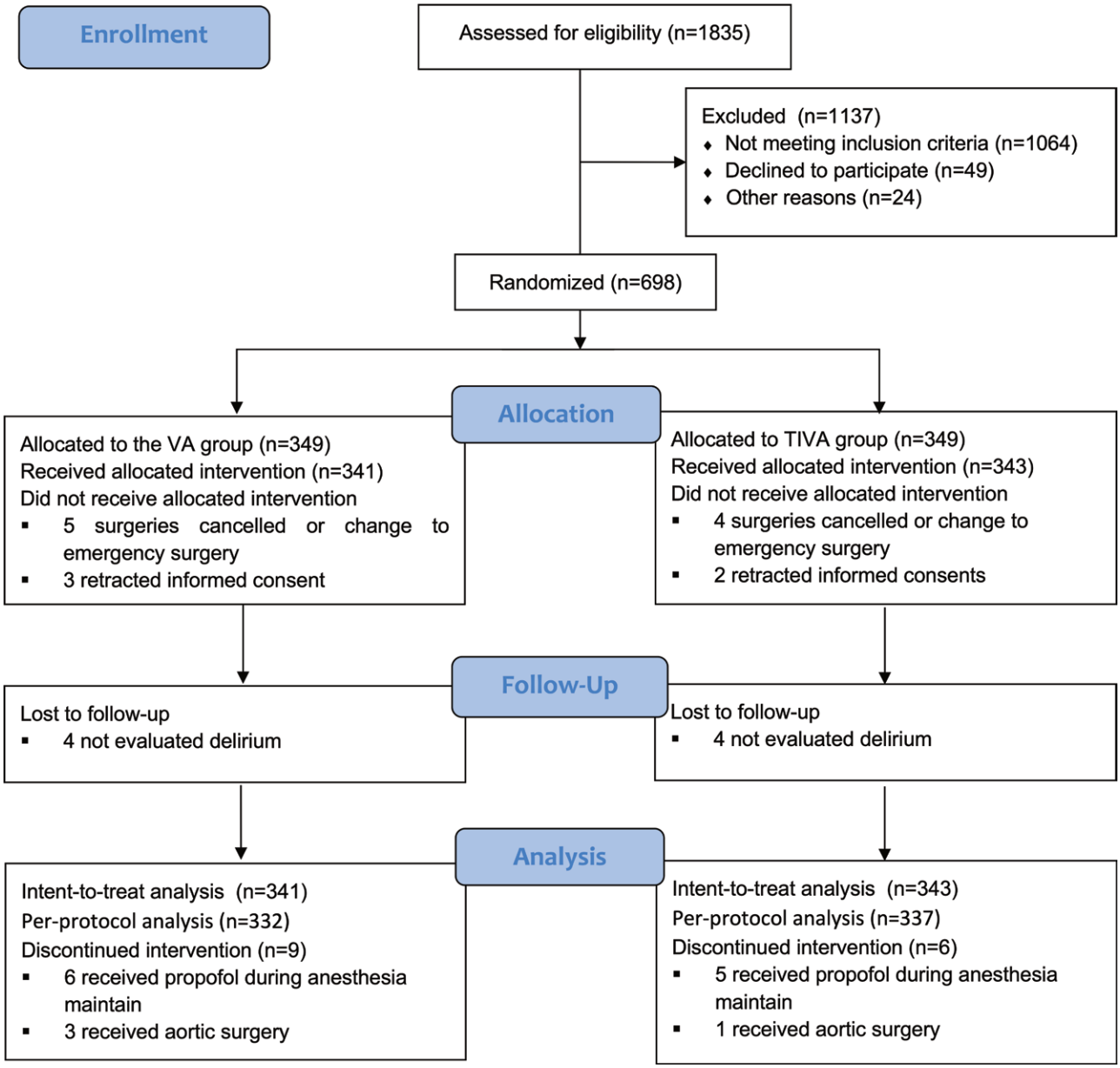

Figure 1. CONSORT diagram of study participant flow. CONSORT indicates Consolidated Standards of Reporting Trials; TIVA, total intravenous anesthesia; VA, volatile anesthesia.

Therefore, the present study comprised 349 patients in each group accounting for a 5% drop-out rate.

RESULTS

Patient Characteristics

The trial was conducted between February 2019 and January 2021, and final follow-up occurred in February 2021. During the study period, 1835 patients were screened for eligibility, of whom 698 patients were enrolled and randomized. A total of 14 patients dropped out, and 4 patients in each group were missing from the primary outcome analysis due to coma. Therefore, primary outcome data were available for 337 patients in the VA group and 339 patients in the TIVA group (Figure 1).

The details of the demographic and clinical characteristics at baseline were shown in Table 1. Of the 684 patients included, the mean (SD) age was 53.8 (11) years old and 381 (55.7%) were women. Ninety-one (26.7%) patients in the VA group and 110 (32.1%) patients in the TIVA group received high school education or above. Sixty-seven (19.7%) and 50 (14.6%) patients in the 2 groups, respectively, had baseline impaired cognition (defined as a Mini-Cog score of ≤3). In addition, the baseline comorbidities and cardiac operative risk assessed by European System for Cardiac Operative Risk Evaluation (EuroSCORE) were well balanced between the groups.

Intraoperative and postoperative characteristics were listed in Table 2. The data appeared generally comparable between the VA and TIVA groups. The vast majority of patients (98%) received isolated valve surgery. Furthermore, there were no significant differences between the groups with regard to the doses of analgesic and sedative drugs after surgery.

Primary Outcome

The delirium (excluding coma) within the first 7 postoperative days occurred in 63 of 337 (18.7%) patients in the VA group and 76 of 339 (22.4%) in the TIVA group. The incidence of delirium did not differ between the 2 groups (RR, 0.80; [95% CI, 0.55–1.16]; P = .231) in the ITT analysis (Table 3). The PP analysis, based on actual intervention received, also showed no significant difference in delirium occurrence between the 2 groups (RR, 0.80; [95% CI, 0.55–1.17]; P = .248)

Table 1. Patient Characteristics at Baseline

Variables	VA group (n = 341)	TIVA group (n = 343)	Standardized difference[a]
Age, y, mean (SD)	54.1 ± 11.0	53.4 ± 11.2	0.063
Female sex, n (%)	188 (55.1)	193 (56.3)	–0.024
Body mass index, kg/m^2, mean ± SD	23.1 ± 3.3	23.1 ± 3.2	0
Education, n (%)			
Less than high school	250 (73.3)	233 (67.9)	0.118
High school or above	91 (26.7)	110 (32.1)	
Current smoke, n (%)	70 (20.5%)	64 (18.7%)	–0.045
Hypertension, n (%)	56 (16.4)	47 (13.7)	0.076
Diabetes mellitus, n (%)	16 (4.7)	25 (7.3)	–0.110
COPD, n (%)	11 (3.2)	10 (2.9)	0.017
Stroke, n (%)	25 (7.3)	30 (8.7)	–0.052
Atrial fibrillation, n (%)	143 (41.9)	125 (36.4)	0.113
Chronic heart failure, n (%)	102 (29.9)	98 (28.6)	0.029
Previous cardiac surgery, n (%)	16 (4.7)	18 (5.2)	–0.023
Chronic pain condition, n (%)	20 (5.9)	21 (6.1)	–0.008
ASA physical status, n (%)			
II	4 (1.2)	2 (0.6)	0.063
III	337 (98.8)	341 (99.4)	
NYHA classification, n (%)			
I	8 (2.4)	6 (1.8)	0.188
II	115 (33.8)	108 (31.7)	
III	209 (61.5)	207 (60.7)	
IV	6 (1.8)	17 (5.0)	
V	2 (0.6)	3 (0.9)	
Ejection fraction, %, median (IQR)	62 (55–67)	63 (57–67)	–0.146
EuroSCORE, median (IQR)	1 (1–3)	1 (1–3)	0.114
Mini-Cog test, n (%)			
<3	67 (19.7)	50 (14.6)	0.136
≥3	273 (80.3)	293 (85.4)	
The FRAIL scale, n (%)			
Prefrail	123 (36.3)	129 (37.6)	0.109
Frail	11 (3.2)	18 (5.2)	

Data are presented as the mean (SD), median (IQR), or number (percentage).

Abbreviations: ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; NYHA, New York Heart Association; SD, standard deviation; TIVA, total intravenous anesthesia; VA, volatile anesthesia.

[a]Standardized differences were calculated using Cohen d, and the difference in means or proportions was divided by the pooled SDs. Standardized differences ≥0.150 were considered imbalanced.

Table 2. Intraoperative and Postoperative Data

Variables	VA group (n = 341)	TIVA group (n = 343)	Standardized differences
Intraoperative data			
Duration of surgery, min, median (IQR)	237 (205–273)	236(206–275)	–0.061
CPB time, min, median (IQR)	113 (92–149)	115(90–145)	–0.019
Aortic cross-clamp time, min, median (IQR)	82 (63–106)	82(62–109)	0.006
Type of surgery, n (%)			
Single valve	284 (83.3)	296 (86.3)	0.093
Multiple valves	35 (10.3)	26 (7.6)	
Valve and CABG	7 (2.1)	5 (1.5)	
Valve and other procedures[a]	15 (4.4)	16 (4.7)	
Intraoperative blood transfusion, n (%)			
RBC	51 (15.0)	52 (15.2)	–0.006
Plasma	18 (5.3)	19 (5.5)	–0.009
Platelet	57 (16.8)	56 (16.3)	0.013
Postoperative data			
Use of analgesic drugs, n (%)			
Sufentanil	10 (2.9)	10 (2.9)	0
Morphine	205 (60.1)	182 (53.1)	0.142
Use of sedative drugs, n (%)			
Midazolam	40 (11.8)	34 (9.9)	0.061
Propofol	255 (74.8)	233 (67.9)	0.153
Dexmedetomidine	133 (39.0)	122 (35.6)	0.070
Antipsychotic (haloperidol or olanzapine)	11 (3.2)	8 (2.3)	0.055
Postoperative blood transfusion, n (%)			
RBC	109 (32.0)	93 (27.1)	0.108
Plasma	42 (12.3)	43 (12.5)	–0.006
Platelet	14 (4.1)	18 (5.2)	–0.052

Data are presented as the mean (SD), median (IQR), or number (percentage).

Abbreviations: CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; IQR, interquartile range; NYHA, New York Heart Association; RBC, red blood cell; TIVA, total intravenous anesthesia; VA, volatile anesthesia.

[a]Valve and other procedures included valve repair/replacement combined with ventricular septal defect repair, atrial septal defect, or ascending aorta repair.

Table 3. Clinical Outcomes in the ITT Analysis

Variables	VA group (n = 341)	TIVA group (n = 343)	RR (95% CI)	*P* value
Primary outcome				
Delirium, n (%)	63/337 (18.7)	76/339 (22.4)	0.80 (0.55–1.16)	.231
According to type of surgery, n (%)				
Single valve	46/281 (16.4)	63/293 (21.5)	0.72 (0.47–1.09)	.117
Multiple valve	11/34 (32.4)	6/26 (23.1)	1.59 (0.50–5.09)	.429
Valve and CABG	3/7 (42.9)	3/4 (75.0)	0.25 (0.02–3.77)	.545
Valve and other procedures	3/15 (20.0)	4/16 (25.0)	0.75 (0.14–4.10)	>.99
Secondary outcomes				
Delirium length, d, median (IQR)	1 (1–2)	1 (1–2)	—	.293
Subtypes of delirium, n (%)				
Hypoactive type	52/63 (82.5)	67/76 (88.2)	0.64 (0.25–1.65)	.347
Hyperactive type	5/63 (7.9)	6/76 (7.9)	1.0 (0.29–3.46)	>.99
Mixed type	6/63 (9.5)	3/76 (3.9)	2.56 (0.61–10.69)	.299
All cause 30-d mortality, n (%)	3 (0.9)	3 (0.9)	1.00 (0.20–5.02)	.994
Coma within the first 7 d after surgery, n (%)	4 (0.9)	4 (0.9)	1.00 (0.20–5.02)	>.99
Cerebral infarction, n (%)	8 (2.3)	3 (0.9)	2.72 (0.72–10.35)	.142
Respiratory failure, n (%)	39 (11.4)	35 (10.2)	1.14 (0.70–1.84)	.604
Pneumonia, n (%)	82 (24.0)	83 (24.2)	0.99 (0.70–1.41)	.963
Pain score, median (IQR)				
NRS at first day	3 (2–5)	3 (2–5)	–	.723
NRS at second day	2 (2–4)	2 (2–3)	–	.198
NRS at third day	2 (1–3)	2 (1–3)	–	.320
Mechanical ventilation time, h, median (IQR)	16 (11–22)	15 (11–22)	–	.893
ICU stay, h, median (IQR)	49 (41–86)	56 (40–76)	–	.880
Hospital stay, d, median (IQR)	7 (6–9)	7 (6–9)	–	.738

Data are presented as the median (IQR) or number (percentage).

Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; ITT, intensive to treat; NRS, numerical rating scale; RR, relative risk; TIVA, total intravenous anesthesia. VA, volatile anesthesia.

(Supplemental Digital Content 1, Table 1, http://links.lww.com/AA/E77).

Secondary Outcomes

Secondary outcomes were listed in Table 3. Delirium duration was 1 (1–2) day in the VA group and 1 (1–2) day in the TIVA group (P = .293). In both groups, the most common type of delirium was hypoactive, which accounted for 85.6% of the total delirium cases. Furthermore, we did not find any significant difference between the 2 groups in any of the secondary outcomes, including 30-day all-cause mortality, pain score, cerebral infarction, respiratory failure, and pneumonia. Likewise, the duration of mechanical ventilation, lengths of ICU, and hospital stay were similar in both groups. Importantly, the results of the PP analysis were in agreement with those results in the ITT analysis (Supplemental Digital Content 1, Table 1, http://links.lww.com/AA/E77).

In the preplanned exploratory subgroup analysis of primary outcome, there was no significant interaction between the treatments and the subgroups (sex, age, education level, history of stroke, and baseline cognition) (Figure 2). Because of the standardized differences of New York Heart Association (NYHA) classification ≥0.150, a post hoc subgroup analysis of NYHA classification was conducted. The specific results were shown in Supplemental Digital Content 1, Table 2, http://links.lww.com/AA/E77. Sensitivity analyses were considered when the patients who could not be assessed for delirium because of coma were assumed to have incident delirium, which showed there was no significant difference in delirium incidence between the groups. Additionally, time to delirium onset did not significantly differ between the groups (log-rank P = .254) (Figure 3).

DISCUSSION

In this trial, we found no evidence that intraoperative anesthetic maintenance regimen with a volatile anesthetic in adults undergoing cardiac valve surgery with CPB can reduce the incidence of POD when compared with propofol-based TIVA.

Previous meta-analyses and consensus opinions had suggested that the use of volatile anesthetics during cardiac surgery, compared to intravenous anesthetics, would improve survival and reduce the risk of postoperative complications such as postoperative pulmonary and myocardial injury.[10–13] Recently, the MYRIAD Study Group found that volatile anesthetics may reduce the risk of myocardial infarction and cardiac mortality (cardiogenic shock and arrhythmias) at 1 year in patients undergoing elective, isolated CABG surgery.[29] However, the neuroprotective effects of volatile agents remain unclear, especially the effect on

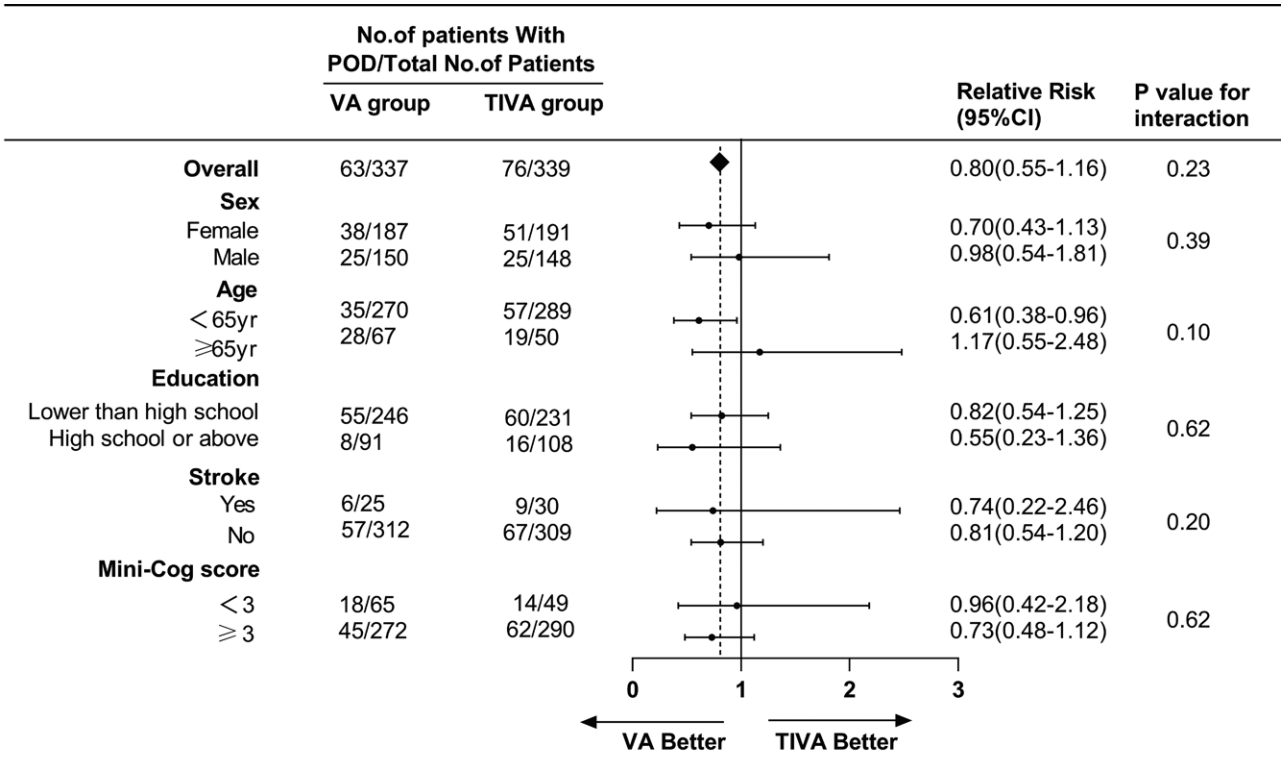

Figure 2. Subgroup analyses of the primary outcome. Relative risk along with 95% CI in each subgroup and P values for interaction between subgroups are presented. CI indicates confidence interval; POD, postoperative delirium; TIVA, total intravenous anesthesia; VA, volatile anesthesia.

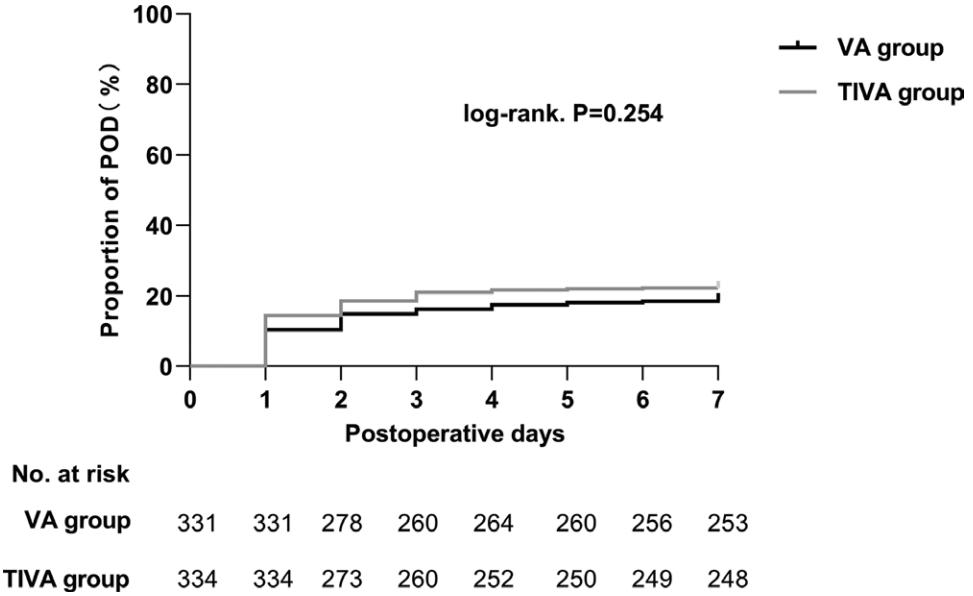

Figure 3. Kaplan-Meier curve describing showing cumulative delirium incidence over postoperative days 1 to 7. The log-rank test indicates no significant difference between the VA group and TIVA group. POD indicates postoperative delirium; TIVA, total intravenous anesthesia; VA, volatile anesthesia.

delirium. In addition, previous research in delirium primarily focused on CABG. As far as we know, this is the first clinical trial to assess the prevalence of delirium in valve surgery patients. Therefore, we consider that the trial has several strengths. First, there is a relatively large sample size compared to previously published trials. Second, our trial is pragmatic and aimed at conducting in real-world settings, which means not interfering with clinical practice to ensure generalizability of trial results. Third, we only included valve surgery, and the effects of the type of surgical procedure on clinical outcomes were minimized. Fourth, the delirium was assessed with the CAM-ICU within the first 7 postoperative days, as recommended by the expert consensus.[30]

In this trial, we failed to demonstrate a significant difference regarding the primary outcome between the 2 anesthesia regimens. The discrepant findings between the current trial and previous studies might partially be explained by the duration of propofol use and the choice of primary outcome. The trial by Schoen et al[31] involving 128 patients undergoing on-pump cardiac surgery compared the effect of different general anesthetics on postoperative cognitive function. They found that sevoflurane-based anesthesia was associated with significantly better postoperative cognitive results. However, their data seemed to be weakened by the fact that patients of both groups received propofol during CPB. In another study by Royse et al,[32] desflurane was associated with a reduced incidence of early postoperative cognitive dysfunction in patients receiving CABG, while no difference in delirium when compared with propofol. Additionally, a prospective randomized controlled study is ongoing (clinicaltrials.gov identifier, NCT03729011), which enrolls elderly patients undergoing cardiac surgery with CPB. The new findings could help complement and refine our interpretations.

Notably, we focused on the patients receiving cardiac valve surgery and found that the rate of delirium was 20.6%. The previous study revealed that compared to CABG, the patients undergoing valve surgery exhibited a high incidence of delirium.[5] Compared with other similar studies, our study population has its own characteristics. The subjects of our study are mainly rheumatic valve disease (RHD) patients, accounting for about 80% of the total cases. The data of 3343 RHD patients from different countries have revealed that this patient population is young and mainly women.[33] In addition, the previous meta-analysis showed that low education level and malnutrition are positively correlated with the risk of RHD, which are also risk factors for delirium.[34] The characteristics of our study population were in line with RHD patients. In our study, the mean age was 53.8 years, 55.7% were women. Additionally, 71.8% of the patients had less than a high school degree, while 17.3% of the patients had college education or above. Overall, these findings provide additional information for future research, especially related to surgical patients with RHD.

In fact, we had hoped that the results were closer to real-world situations, and thus, some aspects of perioperative management were left to the discretion of the medical staff. We did not restrict the use of midazolam and dexmedetomidine. Midazolam was routinely used during cardiac surgery in our hospital due to its hemodynamic profiles. In previous guidelines,

benzodiazepines were not recommended for routine premedication and perioperative use because of the increased risk of POD.[35] Of note, the current Enhanced Recovery after Surgery (ERAS) Society guidelines did not provide a recommendation either for or against the use of benzodiazepines,[36] which may reflect a lack of enough supportive evidence. Regarding dexmedetomidine, a meta-analysis has believed the beneficial effects of perioperative administration for reducing the incidence of delirium after cardiac surgery.[37] However, a recent multicenter study, including 798 patients receiving cardiac surgery, failed to confirm these results.[38] Another factor that may have influenced the results of our trial was the use of propofol in some patients during the ICU stay, which may lead to the weakening of the potential beneficial effect of volatile anesthetics. Practice variability in perioperative care was minimized with a protocolized cardiac surgical environment, and preservation of randomization would be expected to minimize confounding from any anesthetic practice difference. There was no statistical difference regarding the use of midazolam, dexmedetomidine, propofol, and other medicines between the 2 groups.

There are several limitations in this study. First, we only investigated the incidence, duration, and subtype of delirium. But, the severity of delirium was not assessed, and the difference between the 2 groups remained unknown. Second, this was a single-center trial with a restrictive conclusion, which may generate some limitations on generalizability. The results should be replicated in a larger multicenter trial. Third, delirium is sudden severe confusion due to rapid changes in brain function. Intermittent assessment may underestimate the incidence of delirium. Recently published research recommended that delirium assessment should be performed twice a day, which is helpful for identification and treatment.[39] Nevertheless, the daily routine test is still an acceptable method to diagnose delirium at present.[30]

In summary, among adult patients undergoing cardiac valve surgery with CPB, the administration of volatile anesthetics for anesthesia maintenance, compared with propofol-based TIVA, did not decrease the incidence of delirium within the first 7 postoperative days.

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Name: Jia-Li Jiang, MD.
Contribution: This author helped design the study, analyze the data, and prepare the manuscript.
Name: Lu Zhang, MD.
Contribution: This author helped design the study and prepare the manuscript.
Name: Lei-Lei He, MD.
Contribution: This author helped collect the data.
Name: Hong Yu, MD.
Contribution: This author helped collect the data.
Name: Xue-Fei Li, MD.
Contribution: This author helped analyze the data.
Name: Shun-Hui Dai, BSN.
Contribution: This author helped collect the data.
Name: Hai Yu, MD, PhD.
Contribution: This author helped design the study and prepare the manuscript.
This manuscript was handled by: Stefan G. De Hert, MD.

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E临床研究报告原件

挥发性与全静脉麻醉对接受心脏瓣膜手术的成年患者术后谵妄的影响:一项随机临床试验

Jiang Jia-Li, MD，* Lu Zhang, MD，* Lei-Lei He, MD，†Yu Hong, MD，* Xue-Fei Li, MD，* Shun-Hui Dai, BSN，* and Hai Yu, MD, PhD*

背景:麻醉方案对心脏瓣膜置换术后谵妄的影响尚未确定。本研究旨在评价挥发性麻醉与异丙酚全静脉麻醉(TIVA)对心脏瓣膜置换术后谵语发生的影响。

方法:该随机临床试验于2019年2月至2021年1月在中国某高校学术医院进行。计划进行体外泵心脏瓣膜手术或瓣膜联合冠状动脉搭桥术(CABG)手术的患者被随机分配到使用挥发性麻醉剂(七氟醚或地氟醚)或基于异丙酚的TIVA进行麻醉维持。主要转归为术后头7天谵妄发生率，采用重症监护病房(ICU)的精神混乱评估方法进行评估。次要结果包括谵妄持续时间、谵妄分型、30天死亡率、疼痛评分、主要发病率(包括脑梗死、呼吸衰竭和肺炎)、机械通气持续时间、ICU和住院时间。对主要结局变量进行Pearson χ统计分析²测试

结果:在分析的684例患者中(平均年龄53.8岁;381例[55.7%]女性)，676例评估主要结局。337例挥发性麻醉患者中有63例(18.7%)发生术后谵妄，而339例丙泊酚为基础的TIVA患者中有76例(22.4%)发生谵妄(相对风险0.80;95%可信区间[CI]，0.55-1.16;*P* = *.231)*。在任何次要结果中，两组之间都没有显著差异。

结论:在接受体外泵心脏瓣膜手术的患者中，使用挥发性药物的麻醉维持与基于异丙酚的TIVA相比，并没有显著减少术后谵语的发生。(Anesth Analg 2022; 00:00-00)

重点

- 问题:与静脉麻醉相比，挥发性麻醉能减少体外泵心脏瓣膜手术后谵语的发生吗?
- 发现:与以异丙酚为基础的静脉麻醉相比，使用挥发性药物的麻醉维持并没有导致接受心脏瓣膜泵手术的患者术后谵语的病例减少。
- 意义:我们的数据没有提供足够的证据证明选择挥发性麻醉或静脉麻醉会影响泵送心脏瓣膜手术后出现谵妄的风险。

术语表

美国麻醉师协会;冠状动脉搭桥术;混乱评估法;CI =置信区间;报告试验的综合标准;慢性阻塞性肺病;CPB =体外循环;ERAS =增强术后恢复;欧洲心脏手术风险评估系统ICU =重症监护病房;IQR =四分位间距;想要治疗;MAC =最小肺泡浓度;NRS =数值评定量表;纽约心脏协会;术后谵妄;PP =每协议;

四川大学华西医院麻醉科*，成都;四川金鑫妇女儿童医院麻醉科，四川成都。2022年8月26日接受出版。

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j - l。姜浩和张璐对这项工作贡献相当。

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临床试验号:ChiCTR1900021355。

通讯地址:四川大学华西医院麻醉科海宇，医学博士，四川成都610041。发送电子邮件至yuhai@scu.edu.cn。

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列治文焦虑镇静量表;RBC =红细胞;风湿性瓣膜病;相对风险;SD =标准差;TIVA =全静脉麻醉;挥发性麻醉

仅在中国，就有超过18万人接受了体外循环心脏手术(CPB)每年。在成人心脏手术患者中，瓣膜手术是最常见的手术，它代表了一个重要的患者群体，值得研究和考虑。[1]
尽管在手术技术、麻醉管理和围手术期护理方面取得了进步，与心脏手术相关的发病率仍然很高。[2]

术后谵妄(POD)是心脏手术后常见的并发症，发生率为26%至52%，[3]
以意识、注意力、认知或知觉紊乱为特征的[4]
与单纯冠状动脉搭桥术(CABG)患者相比，瓣膜置换术患者发生POD的风险更高。[5]
值得注意的是，经历谵妄的患者恢复受损，住院时间延长，功能和认知能力下降，发病率和死亡率较高，费用增加。[6]
在不同的手术环境(心脏和非心脏手术)的干预表明，谵妄的减少可以改善临床结果和降低成本。[7–9]
随着围手术期医学的快速发展和对谵妄及其决定因素的深入了解，预防和治疗策略是非常必要的。

虽然全身麻醉是心脏手术的标准麻醉技术，但关于麻醉方案和术后结果有不同的证据。一些meta分析和研究评估了麻醉方案对心脏手术相关死亡率和发病率的影响，并报告了混合结果。[10–14]
然而，这些研究并没有报道对谵妄的影响。即便如此，一项对接受心脏手术患者的13项随机试验的荟萃分析显示，挥发性麻醉(VA)比全静脉麻醉(TIVA)提供更好的脑保护。[15]
此外，有限证据表明VA可降低心脏手术患者脑损伤生化标志物水平和术后神经认知功能障碍的发生率。[16]
然而，最近的一项系统综述并没有发现挥发性麻醉药可能减少心脏手术后谵妄的发生。[17]
不幸的是，所有发表的研究都有明显的局限性，阻碍了明确的结论。两种麻醉方案在心脏瓣膜手术后发生急性脑功能障碍或认知障碍风险方面的差异尚不清楚。

因此，我们进行了这项随机临床试验，以评估VA与基于异丙酚的TIVA对心脏瓣膜置换术后谵妄发生的影响。我们假设VA作为一种维持型麻醉可以降低术后头7天内谵语的发生率。

方法

研究设计

这是一个单中心、实用、随机对照试验，有两个平行组。本试验经四川大学华西医院伦理委员会批准(伦理委员会2018号[561])，并在中国临床试验注册中心注册(ChiCTR1900021355，主研究员:于海，注册日期:2019年2月16日。http://www.chictr.org.cn/show-project.aspx?proj=36071.)。这项研究是根据《赫尔辛基宣言》确立的标准完成的，[18]
并获得所有参与者的书面知情同意。本报告遵循平行组随机试验报告综合标准(CONSORT)声明。[19]

参与者

年龄在18岁或以上的成人患者接受选择性的心脏泵入瓣膜手术或瓣膜联合冠脉搭桥手术。排除标准是由于视觉、听觉或语言障碍无法有效沟通;美国麻醉师协会IV级或以上;有神经外科或脑外伤史、癫痫、帕金森病、痴呆、精神分裂症、抑郁症或酗酒史;有服用苯二氮卓类药物、主要镇定剂或类固醇的既往史;严重肝功能不全(Child-Pugh C型);肾衰竭需要透析;并怀疑对研究药物过敏或恶性热疗。

随机化和盲法

书面知情同意书后，根据SPSS 22.0生成的随机分配表，将患者按1:1随机分配至VA组或TIVA组。随机编码保存在按顺序编号的不透明信封中，并在手术前一天发送给研究小组的一名研究协调员。协调器将组分配信息传递给

负责病人护理的麻醉师没有参与这项研究。一名研究者负责患者筛查、登记和术前神经系统评估。结果评估者负责术后随访。患者、外科医生、重症监护医生、结果评估人员和统计人员对组分配不知情。

干预措施

VA组患者在维持麻醉(包括体外循环)期间以最小潮末浓度0.5 ~ 2最小肺泡浓度(MAC)接受七氟醚或地氟醚。TIVA组患者以3 ~ 8 mg • kg输注异丙酚$^{-1}$ • h^{-1}在整个过程中。七氟醚、地氟醚或异丙酚浓度，允许在短时间内超过规定的速率，滴定达到目标双谱指标值40至60。

围手术期管理

咪达唑仑、舒芬太尼、顺阿曲库铵全身麻醉，必要时联合依托咪酯。除挥发性麻醉药或异丙酚外，持续输注瑞芬太尼、间歇输注舒芬太尼和顺阿曲库铵维持麻醉。患者接受标准的机构监测，包括心电图、体温、有创血压、中心静脉压和经食管超声心动图。泵设备包括一个滚筒泵，膜氧合器(美敦力)和油管系统。非脉动流量维持在2.2 ~ 2.4 L • min之间$^{-1}$ • (m)^{2})$^{-1}$。体外循环维持体温32 ~ 34℃，平均动脉压维持在50 ~ 80 mm Hg，体外循环后用鱼精蛋白逆转抗凝作用。

手术后，患者被转移到重症监护病房(ICU)进行额外的护理。术后护理由ICU重症监护医师自行决定。当患者体温正常，自主呼吸，意识清醒，血流动力学稳定时考虑拔管。给患者注射异丙酚或右美托咪定直至达到ICU拔管标准。

结果测量

主要结果。主要转归是术后头7天内谵妄的发生率。术后第1 ~ 7天采用ICU (CAM-ICU)精神混乱评估方法，每天1次(15:00-17:00)。如术后7天内出院，则在出院当天进行最后一次评估。

CAM-ICU是一种针对ICU患者的特异性评估工具，具有较高的敏感性和特异性。[20] CAM-ICU对谵妄的定义有4个特征:(1)精神状态变化或波动的急性发作;(2)注意力不集中;(3)思维混乱;(4)意识水平改变。如果患者同时表现出1和2的特征，同时还表现出3或4的附加特征，他或她就被认为是谵妄。[21] 评估过程分为两个步骤。第一步:用列治文焦虑镇静量表(RASS)评估意识水平;第二步:利用CAM-ICU评估意识内容。仅当RASS评分为> -4时，由CAM-ICU评估谵妄。

次要结果。次要结果包括谵妄持续时间、谵妄亚型、30天全因死亡率、术后前3天疼痛评分、主要发病率(包括脑梗死、呼吸衰竭和肺炎)、机械通气持续时间、ICU和住院时间。通过RASS评分可以确定谵妄的亚型:低活动性型，RASS评分<0;多动型，RASS评分>0;混合型，低活跃型和多活跃型交替发生。[22] 疼痛强度采用数值评定量表(NRS)进行评估。

统计分析

所有的分析都是根据意向治疗原则进行的。对结果也进行了按方案(PP)分析。采用描述性分析来描述基线特征。提出标准化差异，标准化差异变量>1.96 √[(1/n_1) + (1/n_2被认为是不平衡的。[23] 本研究认为标准化差异≥0.150为不平衡。每个变量缺失值的频率和百分比被收集，分析，并在必要时报告。分布正态性采用Kolmogorov-Smirnov检验进行评估。连续变量根据分布以均值(标准差[SD])或中位数(四分位数范围)表示。连续变量组间比较采用独立学生t检验或Mann-Whitney U检验。分类资料以百分数表示。皮尔逊 χ^2 组间比较采用检验。Fisher精确检验仅在至少25%的细胞期望计数<5时使用。时间-事件结果采用Kaplan-Meier生存分析，组间差异采用log-rank检验。在预先指定的亚组中评估治疗效果对主要结局的异质性

将交互项添加到逻辑回归模型中。治疗和每个变量之间的交互作用，包括性别，年龄，教育水平，卒中史和基线认知，分别进行了测试。敏感性分析包括将在所有现场评估中处于昏迷状态的患者加入谵妄组，因为一些人认为昏迷是一种严重的急性脑损伤。[24]

结果以95%置信区间(ci)的相对风险(RRs)表示。所有的分析都是使用Windows (SPSS Inc)的SPSS统计22.0版本进行的。一个双面P值<。0.05被认为具有统计学意义，除非P <.001。

本研究旨在检测VA组和TIVA组术后7天内谵妄发生率的差异。根据我们的临床观察和科学文献中发表的谵妄研究，[25–27]以异丙酚为基础的TIVA治疗下心脏手术后谵妄的发生率假定为25%。计算样本量为每组332例患者，功率为80% (β = 0.2)，显著水平(α)为0.05，表明两组主要结局相对减少35%(绝对减少8.75%)。先前的一项研究表明，谵妄发生率的降低超过基线率的至少1 / 3被认为是临床相关的。[28]

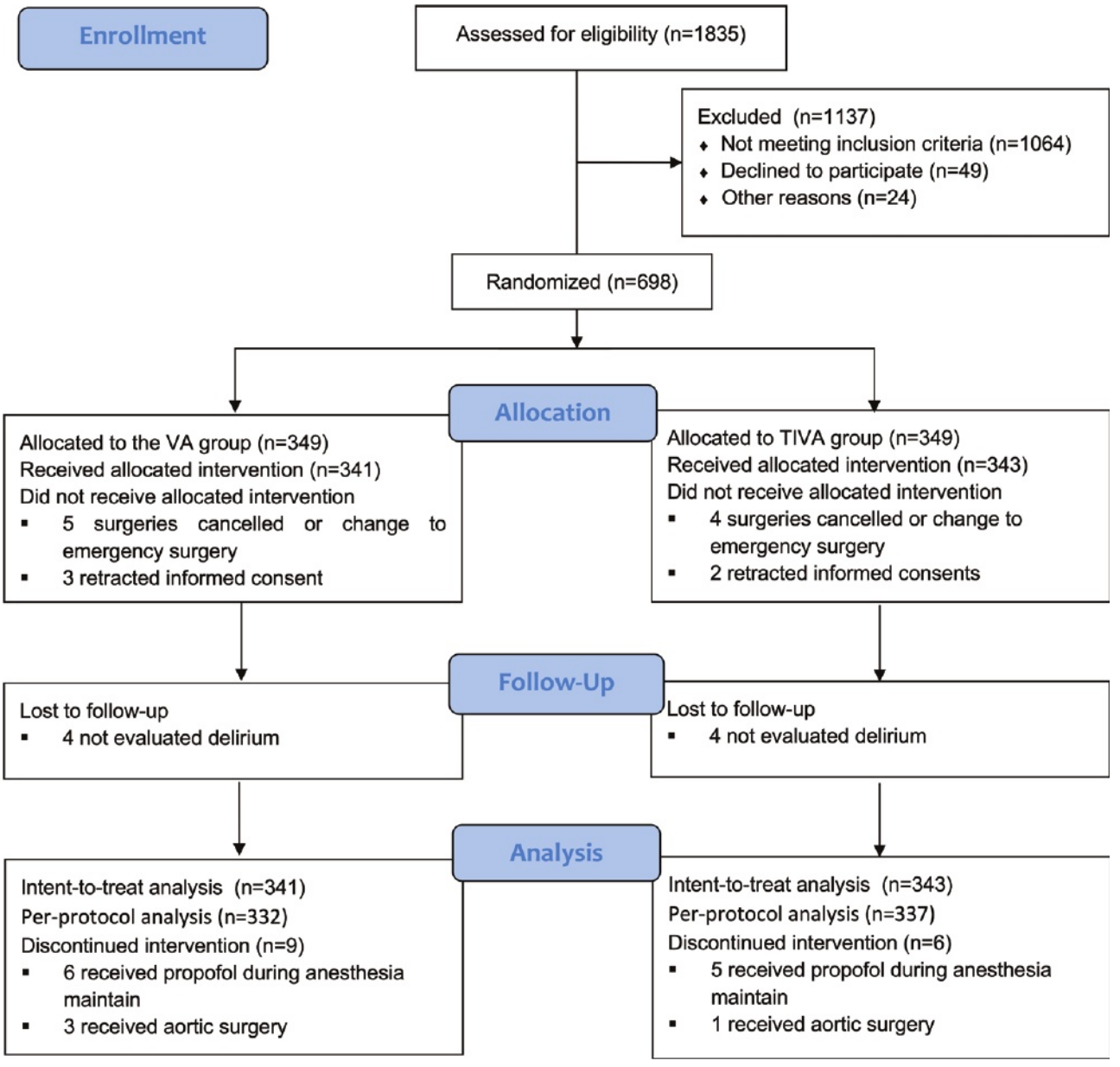

图1。研究参与者流的CONSORT图。CONSORT表示报告试验的综合标准;TIVA，全静脉麻醉;VA，挥发性麻醉。

因此，本研究每组349例，退出率为5%。

结果

患者特征

该试验于2019年2月至2021年1月进行，最后一次随访于2021年2月。在研究期间，筛选了1835名患者，其中698名患者被随机纳入。共有14例患者退出，每组4例患者因昏迷从主要结局分析中缺失。因此，VA组337例患者和TIVA组339例患者可获得主要结局数据(图1)。

基线时的人口统计学和临床特征细节见表1。在纳入的684例患者中，平均(SD)年龄为53.8(11)岁，其中381例(55.7%)为女性。VA组91例(26.7%)和TIVA组110例(32.1%)患者接受高中及以上学历。两组患者分别有67例(19.7%)和50例(14.6%)有基线认知功能受损(Mini-Cog评分≤3分)。此外，由欧洲心脏手术风险评估系统(EuroSCORE)评估的基线共病和心脏手术风险在两组之间很好地平衡。

术中及术后特点见表2。VA组和TIVA组的数据大致相当。绝大多数患者(98%)接受了孤立性瓣膜手术。此外，术后镇痛和镇静药物的剂量组间无显著差异。

主要结果

VA组337例患者中有63例(18.7%)发生谵妄(不包括昏迷)，TIVA组339例患者中有76例(22.4%)发生谵妄。两组谵妄发生率差异无统计学意义(RR, 0.80;[95%可信区间，0.55-1.16];*P = .231)。根据接受的实际干预，PP分析也显示，两组谵妄发生率无显著差异(RR, 0.80;*[95% ci, 0.55-1.17];*P = 0.248)*

表1。患者基线特征

变量VA组(n = 341) TIVA组(n = 343)年龄，y，平均(SD) 54.1±11.0 53.4±11.2女性，n(%) 188(55.1) 193(56.3)体重指数，kg/m2，平均±SD 23.1±3.3 23.1±3.2教育程度，n (%)			标准化差异
高中以下250 (73.3)233 (67.9)			0.063
高中及以上91(26.7)110(32.1)电流吸烟，n(%) 70(20.5%) 64(18.7%)高血压，n(%) 56(16.4) 47(13.7)糖尿病，n (%) 16 (4.7) 25 (7.3) COPD, n(%) 11(3.2) 10(2.9)中风，n(%) 25(7.3) 30(8.7)房颤，n(%) 143(41.9) 125(36.4)慢性心力衰竭，n(%) 102(29.9) 98(28.6)既往心脏手术，n(%) 16(4.7) 18(5.2)慢性疼痛情况，n (%) 20 (5.9) 21 (6.1) ASA身体状况，n (%)			-0.024
Ii 4 (1.2) 2 (0.6)			0
III 337 (98.8) 341 (99.4) NYHA分级，n (%)			0.118
i8 (2.4) 6 (1.8)			-0.045
Ii 115 (33.8) 108 (31.7)			0.076
			-0.110
			0.017
			-0.052
			0.113
			0.029
iii			
	209 (61.5) 207 (60.7)		
iv			
	6 (1.8) 17 (5.0)		
v			
	2 (0.6) 3 (0.9)		
射血分数，%，中位数(IQR) 62 (55-67) 63 (57-67) EuroSCORE，中位数(IQR) 1 (1 - 3) 1 (1 - 3) Mini-Cog test, n (%)			-0.146
<3 67(19.7) 50(14.6)≥3 273(80.3)293(85.4)体质量表，n (%)			0.114
preweak 123 (36.3) 129 (37.6)			0.136
			0.100
体弱11 (3.2)18 (5.2)			

数据以平均值(SD)、中位数(IQR)或数字(百分比)表示。

缩写:ASA，美国麻醉师协会;慢性阻塞性肺病;欧洲心脏手术风险评估系统;IQR，四分位间距;NYHA，纽约心脏协会;SD:标准差;TIVA，全静脉麻醉;VA，挥发性麻醉。[a]使用Cohen d计算标准化差异，将平均值或比例的差异除以汇集的SDs。标准差异≥0.150被认为是不平衡的。

表2。术中及术后资料

变量	VA组(n = 341)	TIVA组(n = 343)	标准化差异
术中资料			
手术时间，min，中位数(IQR)	237 (205-273)	236(206-275)	-0.061
CPB时间，最小值，中值(IQR)	113 (92-149)	115(90-145)	-0.019
啊?Rtic交叉钳时间，最小值，中值(iqr)	82 (63-106)	82(62-109)	0.006
手术类型，n (%)			
单阀	284 (83.3)	296 (86.3)	0.093
多个阀门	35 (10.3)	26 (7.6)	
阀门和CABG	7 (2.1)	5 (1.5)	
阀门及其它程序	15 (4.4)	16 (4.7)	
术中输血，n (%)			
红细胞	51 (15.0)	52 (15.2)	-0.006
等离子体	18 (5.3)	19 (5.5)	-0.009
血小板	57 (16.8)	56 (16.3)	0.013
术后资料			
镇痛药物使用情况(n (%))			
舒芬太尼	10 (2.9)	10 (2.9)	0
吗啡	205 (60.1)	182 (53.1)	0.142
镇静药物使用情况，n (%)			
咪达唑仑	40 (11.8)	34 (9.9)	0.061
异丙酚	255 (74.8)	233 (67.9)	0.153
右美托咪定	133 (39.0)	122 (35.6)	0.070
?抗精神病药(氟哌啶醇或奥氮平)	11 (3.2)	8 (2.3)	0.055
术后输血，n (%)			
红细胞	109 (32.0)	93 (27.1)	0.108
等离子体	42 (12.3)	43 (12.5)	-0.006
血小板	14 (4.1)	18 (5.2)	-0.052

数据以平均值(SD)、中位数(IQR)或数字(百分比)表示。

缩写:CABG，冠状动脉旁路移植术;CPB，体外循环;IQR，四分位间距;NYHA，纽约心脏协会;RBC:红细胞;TIVA，全静脉麻醉;VA，挥发性麻醉。

[a]瓣膜和其他手术包括瓣膜修复/置换联合室间隔缺损修复、房间隔缺损修复或升主动脉修复。

表3。ITT分析中的临床结果

变量VA组(n = 341) TIVA组(n = 343) RR (95% CI) P值主要结局

谵妄，n(%) 63/337(18.7) 76/339(22.4) 0.80(0.55-1.16)。231根据手术类型，n (%)

单阀46/281(16.4)63/293(21.5)0.72(0.47-1.09).117多阀11/34(32.4)6/26(23.1)1.59(0.50-5.09).429阀和CABG 3/7(42.9) 3/4(75.0) 0.25(0.02-3.77) .545阀和其他程序3/15 (20.0)4/16(25.0) 0.75(0.14-4.10) >。99个次要结果

谵妄长度，d，中位数(IQR) 1(1 - 2) 1(1 - 2) - .293谵妄亚型，n (%)

低活跃型52/63(82.5)67/76(88.2)0.64(0.25-1.65).347高活跃型5/63(7.9)6/76(7.9)1.0(0.29-3.46)>。99混合型6/63(9.5)3/76(3.9)2.56(0.61-10.69)。299所有原因30 d死亡率，n(%) 3(0.9) 3(0.9) 1.00(0.20-5.02)。994术后前7 d昏迷，n(%) 4(0.9) 4(0.9) 1.00(0.20-5.02) >。99脑梗死，n(%) 8(2.3) 3(0.9) 2.72(0.72-10.35) .142呼吸衰竭，n(%) 39(11.4) 35(10.2) 1.14(0.70-1.84) .604肺炎，n(%) 82(24.0) 83(24.2) 0.99(0.70-1.41) .963疼痛评分中位数(IQR)

第1天NRS(2 - 5) 3(2 - 5) - .723(2 - 4) 2(2 - 3) - .198(2 - 3) 2(1-3) - .320机械通气时间，h，中位数(IQR) 16(11-22) 15(11-22) - .893个ICU住院时间，h，中位数(IQR) 49(41-86) 56(40-76) - .880个住院时间，d，中位数(IQR) 7 (6-9) 7 (6-9) - .738			

数据以中位数(IQR)或数字(百分比)表示。

缩写:CABG，冠状动脉旁路移植术;CI，置信区间;ICU，重症监护病房;IQR，四分位间距;ITT，强化治疗;NRS，数值评定量表;RR，相对风险;TIVA，全静脉麻醉。VA，挥发性麻醉。

(补充数字内容1，表1,http://links.lww.com/AA/E77)。

次要结果

次要结果列于表3。VA组谵妄持续时间为1(1 - 2)天，TIVA组谵妄持续时间为1(1 - 2)天(P = .293)。在两组中，最常见的谵妄类型为低活动性，占谵妄病例总数的85.6%。此外，我们没有发现两组在任何次要结果(包括30天全因死亡率、疼痛评分、脑梗死、呼吸衰竭和肺炎)方面有任何显著差异。同样，两组患者的机械通气时间、ICU时间和住院时间相似。重要的是，PP分析的结果与ITT分析的结果一致(补充数字内容1，表1,http://links.lww.com/AA/E77)。

在主要结局的预计划探索性亚组分析中，治疗与亚组(性别、年龄、教育水平、卒中史和基线认知)之间没有显著的相互作用(图2)。由于纽约心脏协会(NYHA)分类的标准化差异≥0.150，我们进行了NYHA分类的事后亚组分析。具体结果见附录数字内容1，表2,http://links.lww.com/AA/E77。当因昏迷而不能评估谵妄的患者被假定为谵妄事件时，考虑敏感性分析，结果显示两组间谵妄发生率无显著差异。此外，两组间谵妄发作时间无显著差异(log-rank P = .254)(图3)。

讨论

在本试验中，我们没有发现任何证据表明，与基于异丙酚的TIVA相比，在进行心脏瓣膜手术的成年人中，使用挥发性麻醉药的术中麻醉维持方案可以降低过氧化物酶的发生率。

之前的荟萃分析和共识意见都认为，与静脉麻醉相比，在心脏手术中使用挥发性麻醉药可以提高存活率，并降低术后并发症的风险，如术后肺和心肌损伤。[10–13]
最近，MYRIAD研究组发现，挥发性麻醉剂可降低接受择期、孤立CABG手术的患者1年心肌梗死和心脏死亡(心源性休克和心律失常)的风险。[29]
然而，挥发性药物的神经保护作用仍不清楚，特别是对

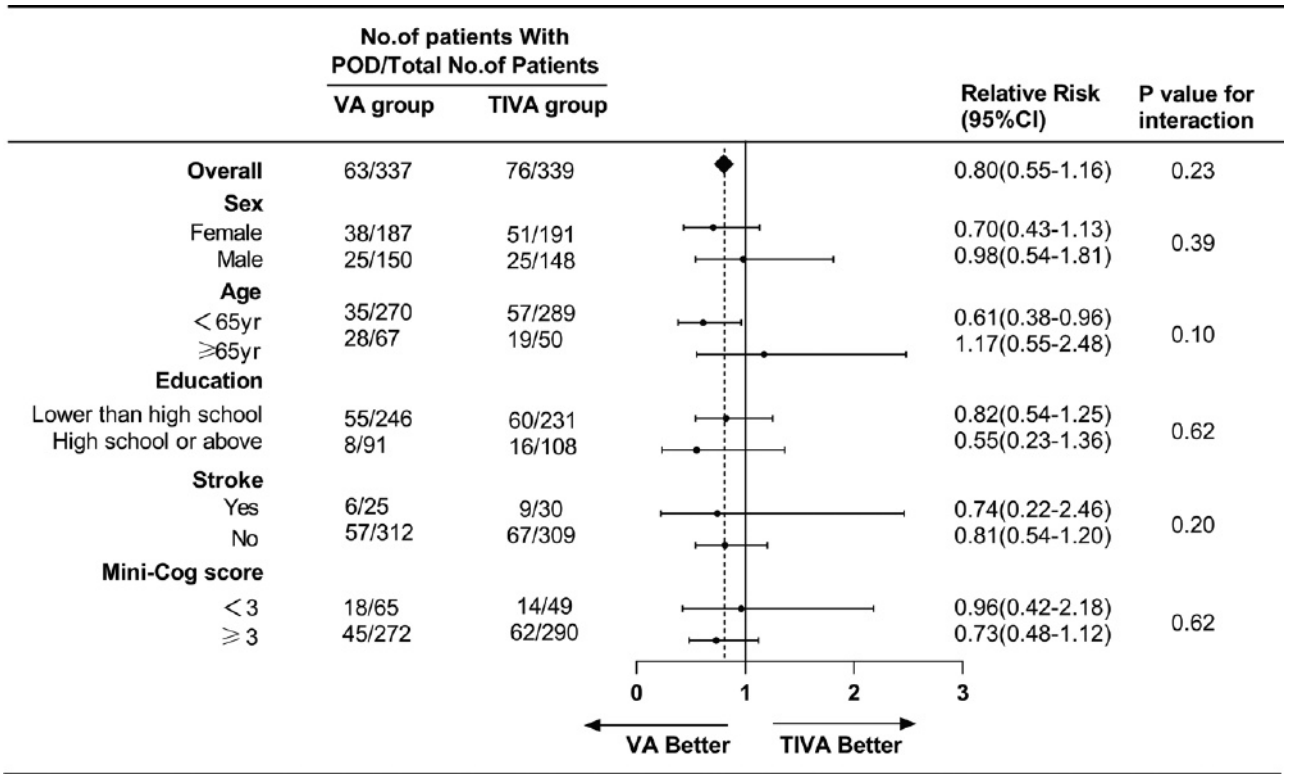

图2。主要结果的亚组分析。给出了各亚组的相对风险、95% CI以及亚组间相互作用的P值。CI表示置信区间;POD:术后谵妄;TIVA，全静脉麻醉;VA，挥发性麻醉。

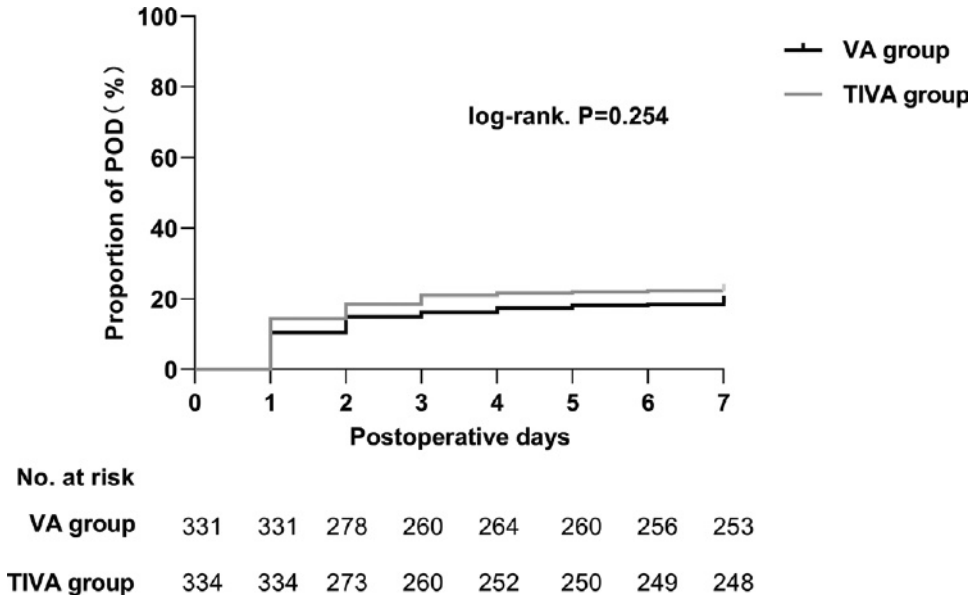

图3。描述术后1 - 7天谵妄累积发生率的Kaplan-Meier曲线。log-rank检验显示VA组与TIVA组无显著性差异。POD提示术后谵妄;TIVA，全静脉麻醉;VA，挥发性麻醉。

谵妄此外，先前对谵妄的研究主要集中在CABG上。据我们所知，这是第一个评估瓣膜手术患者谵妄发生率的临床试验。因此，我们认为审判有几个优点。首先，与之前发表的试验相比，该试验的样本量相对较大。其次，我们的试验是务实的，目的是在现实环境中进行，这意味着不干预临床实践，以确保试验结果的普遍性。第三，我们只包括瓣膜手术，手术方式对临床结果的影响被最小化。第四，按照专家共识建议，在术后头7天内，在CAM-ICU进行谵妄评估。[30]

在本试验中，我们未能证明两种麻醉方案之间的主要结局有显著差异。目前的试验和以前的研究之间的差异可能部分解释了异丙酚使用的持续时间和主要结果的选择。Schoen等人的试验[31]
128例接受心脏泵浦手术的患者比较了不同全身麻醉药对术后认知功能的影响。他们发现以七氟醚为基础的麻醉与术后明显更好的认知结果相关。然而，他们的数据似乎被两组患者在体外循环中接受异丙酚的事实所削弱。在罗伊斯等人的另一项研究中，[32]
地氟醚与CABG患者术后早期认知功能障碍发生率降低相关，而与异丙酚相比谵妄发生率无差异。此外，一项前瞻性随机对照研究正在进行中

(clinicaltrials.gov identifier, NCT03729011)，该网站收录了接受体外循环心脏手术的老年患者。新的发现可以帮助补充和完善我们的解释。

值得注意的是，我们集中研究了接受心脏瓣膜手术的患者，发现谵妄的发生率为20.6%。既往研究显示，与冠脉搭桥相比，接受瓣膜手术的患者谵妄发生率较高。[5]
与其他同类研究相比，我们的研究人群有其自身的特点。我们的研究对象主要是风湿性瓣膜病(rheumatic valve disease, RHD)患者，约占病例总数的80%。来自不同国家的3343名RHD患者的数据显示，这一患者群体是年轻的，主要是女性。[33]
此外，之前的meta分析显示，受教育程度低、营养不良与罹患RHD的风险呈正相关，这也是谵妄的危险因素。[34]
我们的研究人群的特征符合RHD患者。在我们的研究中，平均年龄为53.8岁，55.7%为女性。71.8%的患者学历在高中以下，17.3%的患者学历在大学及以上。总的来说，这些发现为未来的研究提供了更多的信息，特别是与RHD手术患者相关的研究。

事实上，我们希望结果更接近真实情况，因此，围手术期管理的一些方面留给医务人员的自由裁量权。我们没有限制咪达唑仑和右美托咪定的使用。由于咪达唑仑的血流动力学特点，在我院心脏手术中经常使用。在之前的指南中，

由于苯二氮卓类药物增加了过氧化物酶的风险，因此不建议常规用药和围手术期使用。[35]
值得注意的是，当前的强化术后恢复(ERAS)协会指南并没有提供支持或反对使用苯二氮卓类药物的建议，[36]
这可能反映出缺乏足够的支持性证据。关于右美托咪定，一项荟萃分析认为围手术期给药对降低心脏手术后谵妄的发生率有有益作用。[37]
然而，最近的一项多中心研究，包括798名接受心脏手术的患者，未能证实这些结果。[38]
另一个可能影响我们试验结果的因素是，一些患者在ICU住院期间使用了异丙酚，这可能会削弱挥发性麻醉药的潜在有益作用。围手术期护理的实践变异性在心脏手术环境协议中被最小化，保留随机化将被期望最小化任何麻醉实践差异的混淆。咪达唑仑、右美托咪定、异丙酚等药物的使用两组间无统计学差异。

本研究存在几个局限性。首先，我们只调查了谵妄的发生率、持续时间和亚型。但是，谵妄的严重程度未被评估，两组之间的差异仍然未知。其次，这是一个单中心试验，结论具有限制性，可能会产生一定的局限性。该结果应该在更大的多中心试验中得到验证。第三，谵妄是由于大脑功能的快速变化而引起的突然的严重的精神混乱。间歇性评估可能会低估谵妄的发生率。最近发表的研究建议谵妄评估应该每天进行两次，这有助于识别和治疗。[39]
然而，日常常规检查仍是目前可以接受的谵妄诊断方法。[30]

综上所述，在接受心脏瓣膜体外循环手术的成年患者中，与基于异丙酚的TIVA相比，使用挥发性麻醉药进行麻醉维持，并没有降低术后前7天谵语的发生率。e

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披露

姓名:蒋佳丽，医学博士

贡献:帮助设计研究，分析数据，准备稿件。

姓名:张璐，医学博士。

贡献:帮助设计研究并准备稿件。

姓名:何雷磊，医学博士

贡献:帮助收集数据。姓名:于红，医学博士。

贡献:帮助收集数据。姓名:李雪飞，医学博士

贡献:帮助分析数据。姓名:戴顺辉，BSN。

贡献:帮助收集数据。姓名:于海，医学博士，博士。

贡献:帮助设计研究并准备稿件。

手稿由医学博士Stefan G. De Hert处理。

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