

The Effects of Different Doses of Sufentanil on Intraoperative Cardiovascular Response and Postoperative Recovery in Patients Undergoing Cardiac Surgery: A Retrospective Cohort Study

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Objective: To investigate the correlation between the amount of sufentanil used during anesthesia and intraoperative hemodynamic fluctuation and postoperative recovery in patients undergoing cardiopulmonary bypass (CPB).

Materials and Methods: A retrospective analysis was performed on 454 patients undergoing elective heart surgery under CPB. Patients were divided into two groups according to the amount of sufentanil used during anesthesia: Group L (induced sufentanil 0.4–0.6 ug/kg, maintained sufentanil 0.01–0.02 ug/kg/min, n = 223) and Group H (induced sufentanil 4–6 ug/kg, maintained sufentanil 0.02–0.03 ug/kg/min, n = 231). Propensity score matching (PSM) was used at a 1:1 nearest-neighbor ratio to compare the two groups. Intraoperative use of vasoactive drugs, spontaneous heart rebound, secondary endotracheal intubation, postoperative mechanical ventilation time, the length of stay (LOS) in ICU, postoperative LOS in hospital, postoperative in-hospital mortality were analyzed.

Results: After matching, a total of 144 patients were included (72 patients in Group L, and 72 patients in Group H). Multivariate logistic regression analysis showed that the dosage of sufentanil during anesthesia was significantly correlated with the utilization rate of intraoperative vasoactive drugs ($P < 0.001$) and the success rate of spontaneous heart rebound ($p = 0.001$). The utilization rate of vasoactive drugs decreased significantly in Group H (OR, 0.062; 95% CI, 0.019–0.200) compared to that of Group L. The success rate of spontaneous heart rebound (OR, 0.187; 95% CI, 0.071–0.491) was higher in Group H. There were no differences on postoperative recovery outcomes between the two groups.

Conclusion: On the basis of our data, the use of high-dose sufentanil is beneficial to keep the cardiovascular response of patients in a stable state, but there is no significant effect on the quality of early postoperative recovery.

Keywords: sufentanil, extracorporeal circulation, cardiac anesthesia

Cardiovascular disease is the main cause of death in the world, accounting for about 1/3 of all deaths^{1–3} and is characterized by high incidence, high disability and high mortality. China is one of the countries with the highest cardiovascular mortality,^{4,5} and the prevalence is still on the rise, which will lead to more and more people face the risk of cardiac surgery. Cardiopulmonary bypass is one of the main methods of treating organic heart disease, and there are many challenges associated with anesthesia.

Patients undergoing cardiac surgery under CPB have special pathophysiological conditions and exhibit lower tolerance to anesthesia. Median sternotomy, cardiac arrest, and aortic cross-clamping will inevitably lead to systemic inflammatory reactions, causing ischemic damage and electrophysiological damage to myocardial tissue.⁶ In addition, the occurrence of lung injury caused by cardiac insufficiency itself leads to an increase in the incidence of postoperative pulmonary complications and aggravation of symptoms. Sufentanil is the most commonly used opioid in cardiovascular surgery, its analgesic and sedative effect is good, can provide better cardiovascular stability,^{7–10} and reduce the body's

work in the heart and other organs under anesthesia, thereby increasing the functional reserve of the heart. However, its dosage is still controversial.

Opioids are traditionally recommended for cardiac surgery because of their unique ability to maintain hemodynamic stability during anesthesia and improve cardiovascular responses caused by surgical stimulation.¹¹ However, the different doses of perioperative opioids used in surgeries have been associated with adverse events, including somnolence, respiratory depression and cardiopulmonary arrest.^{12,13} The previous study has reported that the recommended sufentanil dose during general anesthesia induction is 0.1 ug/kg, not a higher dose.¹⁴ Bhavsar et al¹⁵ also reported a lower dose of sufentanil, compared with a standard dose, did not enhance fast-track conditions significantly in patients with coronary artery bypass grafting. Recently, the view that opioid-related adverse drug events were previously thought to be more likely to be associated with higher opioid doses is being debated. Some clinical reports have tended to the use of high-dose drugs. Two meta-analyses reported no significant differences were found in the risk of myocardial infarction, stroke, or reintubation when comparing high-dose opioids versus low-dose opioids in cardiac surgery, but low-dose opioid drugs only decreased postoperative intubation time.^{16,17} However, both the analyses were not specifically focused on the dose of opioids used.

The aim of this study is to evaluate the effects of high-dose sufentanil and low-dose sufentanil on cardiovascular response and short-term postoperative recovery in patients undergoing cardiac surgery under CPB. This study helps to determine whether higher doses of opioid use would be associated with greater perioperative adverse outcomes.

Data and Methods

General Information

This study follows the STROBE statement,¹⁸ has been approved by the Medical Ethics Committee of the First People's Hospital of Lianyungang (KY-20220906001-01), and has applied for an informed consent exemption for the subjects. The study protocol complies with the Declaration of Helsinki. The trial was registered prior to enrollment at the Chinese Clinical Trial Registry (ChiCTR2200066713) on 14/12/2022. Patients aged 18–78 years undergoing elective cardiac surgery under CPB from December 2017 to December 2021 were selected. Inclusion criteria: ASA II–IV, surgical procedures included coronary artery bypass grafting (CABG), surgical correction of valvular disease (aortic, mitral, tricuspid, and pulmonary), combined surgery, surgery for ascending aortic disease, mixed surgery, and other cardiac procedures under CPB. Exclusion criteria: 1) patients requiring special induction; 2) participants in other programs; 3) known drug allergy; 4) pregnancy; 5) chronic renal insufficiency (serum creatinine > 2.0 mg/dL) or impaired liver function (serum bilirubin > 1.2 mg/dL) before surgery; 6) patients with a history of drug and alcohol abuse or long-term pain management with preoperative use of non-steroidal anti-inflammatory drug or opioids; and 7) patients with major intraoperative and postoperative indicators being not available through the case system.

Anesthetic Methods

Fasting for 12 h and no drinking for 4 h before surgery.¹⁹ A peripheral venous access was established after the patient was admitted to the room. Electrocardiogram (ECG), oxygen saturation (SpO₂), heart rate (HR), and bispectral index (BIS) were routinely monitored. 1% lidocaine without epinephrine, a 5-cc syringe, and a 25-gauge needle will be needed for delivery of the local anesthetic.²⁰ After local anesthesia, invasive blood pressure (IBP) was monitored by ultrasound-guided radial artery catheterization.

Anesthesia Induction

Midazolam 0.01–0.02 mg/kg, etomidate 0.15–0.30 mg/kg, and cis-atracurium 0.15–0.2 mg/kg were given intravenously. There are two induced doses of sufentanil, and the allocation method is random. The induced dose of sufentanil was 0.4–0.6 ug/kg in low-dose group (Group L), and 4–6 ug/kg in high-dose group (Group H). Under a visual laryngoscope, tracheal intubation was performed and volume-controlled ventilation mode was applied. Respiratory parameters were adjusted, RR 10–15 times/min, I:E = 1:2, and P_{ET}CO₂ 35–45 mmHg was maintained. During surgery, lung protective ventilation strategies were performed before and after CPB (including low-tidal VT 6–8 mL/kg according to ideal body weight, administration of 5 cmH₂O positive end-expiratory pressure,²¹ and timely performance of recruitment maneuver, among others); Adjusting FiO₂²² to enable SPO₂ to be maintained over 92% at a minimum level²³ without pulmonary

ventilation during CPB.²¹ The right internal jugular vein was punctured under the guidance of ultrasound, and a 7F three-lumen central venous catheter was placed to monitor the central venous pressure (CVP).

Anesthesia Maintenance

0.5–1.0% sevoflurane was inhaled, propofol 2–3 mg/kg/h and cis-atracurium 0.06–0.12 mg/kg/h were infused intravenously, BIS 40–60 was maintained as needed during the surgery. Group L was given sufentanil 0.01–0.02 ug/kg/min, Group H was given sufentanil 0.02–0.03 ug/kg/min. Noradrenaline, dopamine, dobutamine, epinephrine, milrinone, nitroglycerin, and other vasoactive drugs were used to maintain hemodynamics as needed intraoperatively. All patients were sent to the adult cardiac intensive care unit (CICU) for further treatment after surgery. When patients had stable hemodynamics, did not need or required little vasoactive medication (Vasoactive-Inotropic Score VIS \leq 10), had adequate gas exchange, and did not have any major complications, such as sepsis, renal insufficiency, and neurological problems, and were conscious enough to maintain their normal ventilation, extubation was permitted.

Data Collection

Gender, age, BMI, ASA classification, type of cardiac surgery, prior comorbidities (personal history) including hypertension, diabetes mellitus, atrial fibrillation, chronic heart failure, previous myocardial infarction within 90 days, pulmonary hypertension, cerebral infarction, operation history, chronic obstructive pulmonary disease (COPD), etc. were collected; preoperative left ventricular ejection fraction (LVEF), the success rate of spontaneous heart rebound during operation, the use of vasoactive drugs, the amount of fluid in and out, the amount of blood loss, the transfusion amounts of allogeneic blood and autologous blood, the operation time, the duration of CPB, the amount of sufentanil used during operation, postoperative short-term prognostic indicators including postoperative complications (pulmonary infection, early postoperative respiratory failure, postoperative bleeding, arrhythmia, cerebral infarction...), time of postoperative mechanical ventilation (extubation time, h), LOS in ICU, LOS in hospital, in-hospital mortality, and second intubation rate after operation were also collected.

Postoperative complications were defined according to the criteria used by the European Society of Anesthesiology.²⁴ Pulmonary infection was defined as a patient with a suspected infection who was prescribed antibiotics and met one or more of the following requirements at the same time: new or changed sputum, new or changed lung shadow, fever, and white blood cell count $> 12 \times 10^9/L$. Early postoperative respiratory failure was defined as $PaO_2/FiO_2 < 200$ during ICU care. The occurrence of short-term postoperative complications can be queried from the patient's in-hospital medical records.

The patients were divided into two groups according to the amount of sufentanil used during the operation: Group L (induced sufentanil 0.4–0.6 ug/kg, maintained sufentanil 0.01–0.02 ug/kg) and Group H (induced sufentanil 4–6 ug/kg, maintained sufentanil 0.02–0.03 ug/kg).

Statistical Analysis

SPSS 25.0 was used for statistical analysis. Propensity score matching (PSM) was performed to reduce the selection deviation and confounding effects between the two groups. Propensity score (PS) was calculated with logistic regression analysis, including covariates such as demographics, preoperative comorbidities, and surgical data. The covariates that have influence on both independent variables and dependent variables are selected for matching. The nearest neighbor method was used for matching at 1:1 (caliper value set to 0.2). After the propensity score was matched, the McNemar test or paired *t*-test was used to analyze the relationship between sufentanil infusion and major and secondary indicators.

Univariate logistic regression was used to analyze the relationship between each variable and positive results. The variables of $P < 0.2$ in univariate analysis were included in multivariate logistic regression to further analyze the correlation between outcome indexes and the use of sufentanil. These factors included NYHA (New York Heart Association function class), preoperative atrial fibrillation, type of operation, EF (ejection fraction), CPB time (cardio-pulmonary bypass time), gender, preoperative smoking history, preoperative pulmonary hypertension. Patients with missing data on any matching factors were excluded from the propensity score matching analysis.

Results

From December 2017 to December 2021, 472 patients underwent open heart surgery under CPB. Of these, 454 patients were ultimately included in the analysis. Low-dose sufentanil was given intraoperatively in 223 patients and high-dose sufentanil was given intraoperatively in 231 patients (Table 1). After propensity score matching, there were 72 patients in each group (Figure 1). Baseline characteristics after propensity score matching were compared as follows (Table 2).

Table 1 Comparison of General Conditions Between the Two Groups Before PSM

Variables	Group L (N=223)	Group H (N=231)	SMD	P-value
Gender, n(%)			0.247	0.012
Female	118 (52.91%)	94 (40.69%)		
Male	105 (47.09%)	137 (59.31%)		
ASA status, n(%)			0.169	0.202
II	12 (5.38%)	8 (3.46%)		
III	121 (54.26%)	112 (48.48%)		
IV	90 (40.36%)	111 (48.05%)		
NYHA, n(%)			0.391	<0.001
I	2 (0.90%)	1 (0.43%)		
2	57 (25.56%)	27 (11.69%)		
3	133 (59.64%)	175 (75.76%)		
4	31 (13.90%)	28 (12.12%)		
Preoperative pulmonary infection, n(%)			0.143	0.165
None	194 (87.00%)	189 (81.82%)		
Yes	29 (13.00%)	42 (18.18%)		
Preoperative hypertension, n(%)			0.236	0.017
None	149 (66.82%)	128 (55.41%)		
Yes	74 (33.18%)	103 (44.59%)		
Preoperative diabetes mellitus, n(%)			0.269	0.007
None	205 (91.93%)	192 (83.12%)		
Yes	18 (8.07%)	39 (16.88%)		
Preoperative atrial fibrillation, n(%)			0.296	0.003
None	142 (63.68%)	178 (77.06%)		
Yes	81 (36.32%)	53 (22.94%)		
Smoker, n(%)			0.099	0.355
None	182 (81.61%)	197 (85.28%)		
Yes	41 (18.39%)	34 (14.72%)		
COPD, n(%)			0.057	0.618
None	221 (99.10%)	230 (99.57%)		
Yes	2 (0.90%)	1 (0.43%)		
Preoperative pulmonary hypertension, n(%)			0.549	<0.001
None	81 (36.32%)	145 (62.77%)		
Yes	142 (63.68%)	86 (37.23%)		
Family history, n(%)			0.002	1.000
None	222 (99.55%)	230 (99.57%)		
Yes	1 (0.45%)	1 (0.43%)		
Type of operation, n(%)			0.847	1.000
Valve	144 (64.57%)	100 (43.29%)		
CABG	5 (2.24%)	70 (30.30%)		
Combined	13 (5.83%)	17 (7.36%)		
Adult heart disease	11 (4.93%)	5 (2.16%)		
Ascending aortic surgery	3 (1.35%)	2 (0.87%)		
Mixed operation and others	47 (21.08%)	37 (16.02%)		
Age (years)	58.00 [49.00, 64.00]	63.00 [54.50, 67.00]	0.472	<0.001
BMI (kg/m ²)	22.89 [21.15, 25.48]	23.88 [21.47, 26.30]	0.191	0.039
EF (%)	60.00 [56.00, 60.00]	60.00 [56.00, 60.00]	0.024	0.799

(Continued)

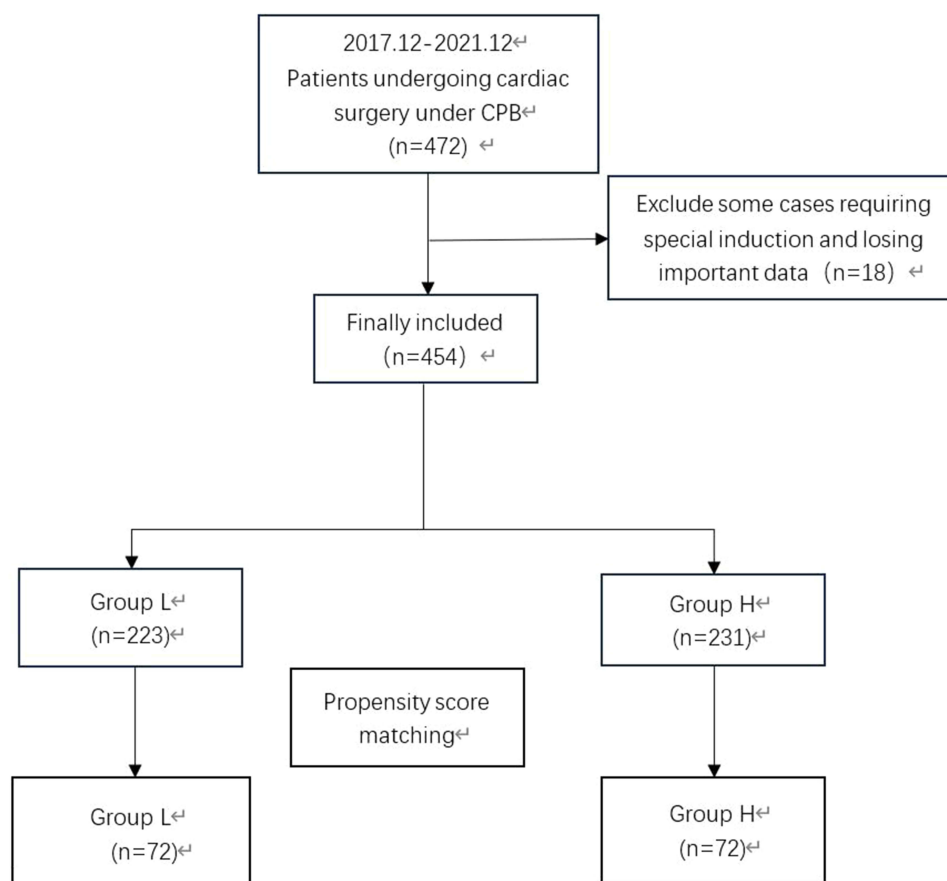
Table I (Continued).

Variables	Group L (N=223)	Group H (N=231)	SMD	P-value
Preoperative hemoglobin (g/l)	137.00 [124.00, 150.00]	133.00 [119.00, 144.50]	0.244	0.019
Intravenous fluid (mL)	1000.00 [700.00, 1000.00]	1650.00 [1100.00, 2200.00]	1.272	<0.001
Intravenous erythrocyte (mL)	0.00 [0.00, 200.00]	0.00 [0.00, 300.00]	0.221	0.142
Autologous blood (mL)	500.00 [0.00, 750.00]	500.00 [250.00, 750.00]	0.268	0.006
Mechanical blood (mL)	0.00 [0.00, 500.00]	1000.00 [500.00, 1200.00]	1.198	<0.001
Blood loss (mL)	300.00 [280.00, 400.00]	400.00 [300.00, 500.00]	0.277	<0.001
Operation time (min)	270.00 [224.00, 315.00]	325.00 [260.00, 381.00]	0.448	<0.001
CPB time (min)	118.00 [92.00, 160.50]	139.00 [105.50, 187.00]	0.244	<0.001

Abbreviations: ASA, American Society of Anesthesiologists; NYHA, New York Heart Association function class; COPD, chronic obstructive pulmonary disease; CABG, Coronary Artery Bypass Grafting; BMI, body mass index; EF, ejection fraction; CPB, cardiopulmonary bypass.

The matching results of the propensity score showed that there were significant differences in the utilization rate of vasoactive drugs ($P < 0.001$) and the heart rebound mode ($P = 0.005$) between high-dose sufentanil group (Group H) and low-dose sufentanil group (Group L). The utilization rate of vasoactive drugs in Group H was significantly lower than that in Group L (Table 3). There were no significant differences in secondary endotracheal intubation ($P = 0.620$), postoperative mechanical ventilation time ($P = 0.701$), postoperative LOS in hospital ($P = 0.685$), LOS in ICU ($P = 0.128$), and postoperative in-hospital mortality ($P = 1.000$) between the two groups (Table 3).

According to the univariate regression analysis, intraoperative sufentanil infusion (OR, 0.078; 95% CI, 0.026, 0.236; $P < 0.001$), preoperative atrial fibrillation (OR, 4.836; 95% CI, 1.384, 16.893; $P = 0.014$), CABG (OR, 0.204; 95% CI, 0.060, 0.696; $P = 0.011$) and CPB time (OR, 1.009; 95% CI, 1.001, 1.017; $P = 0.021$) were significantly related to the utilization rate of vasoactive

**Figure 1** Flowchart of patient selection.

Abbreviation: CPB, cardiopulmonary bypass.

Table 2 Comparison of General Conditions Between the Two Groups After PSM

Variables	Group L (N=72)	Group H (N=72)	SMD	P-value
Gender, n(%)			0.084	0.737
Female	39 (54.17%)	42 (58.33%)		
Male	33 (45.83%)	30 (41.67%)		
ASA-status, n(%)			0.291	0.226
II	6 (8.33%)	5 (6.94%)		
III	38 (52.78%)	48 (66.67%)		
IV	28 (38.89%)	19 (26.39%)		
NYHA, n(%)			0.138	0.863
I	1 (1.39%)	1 (1.39%)		
2	16 (22.22%)	15 (20.83%)		
3	44 (61.11%)	48 (66.67%)		
4	11 (15.28%)	8 (11.11%)		
Preoperative pulmonary infection, n(%)			0.07	0.833
None	57 (79.17%)	59 (81.94%)		
Yes	15 (20.83%)	13 (18.06%)		
Preoperative hypertension, n(%)			0.058	0.862
None	47 (65.28%)	45 (62.50%)		
Yes	25 (34.72%)	27 (37.50%)		
Preoperative diabetes mellitus, n(%)			0.084	0.801
None	64 (88.89%)	62 (86.11%)		
Yes	8 (11.11%)	10 (13.89%)		
Preoperative atrial fibrillation, n(%)			0.032	1.000
None	53 (73.61%)	54 (75.00%)		
Yes	19 (26.39%)	18 (25.00%)		
Smoker, n(%)			0.039	1.000
None	61 (84.72%)	62 (86.11%)		
Yes	11 (15.28%)	10 (13.89%)		
COPD, n(%)			<0.001	1.000
None	71 (98.61%)	71 (98.61%)		
Yes	1 (1.39%)	1 (1.39%)		
Preoperative pulmonary hypertension, n(%)			0.111	0.617
None	35 (48.61%)	39 (54.17%)		
Yes	37 (51.39%)	33 (45.83%)		
Family history, n(%)	72 (100.00%)	72 (100.00%)	<0.001	
Type of operation, n(%)			0.261	0.671
Valve	39 (54.17%)	39 (54.17%)		
CABG	4 (5.56%)	9 (12.50%)		
Combined	6 (8.33%)	5 (6.94%)		
Adult heart disease	4 (5.56%)	3 (4.17%)		
Mixed operation and others	19 (26.39%)	16 (22.22%)		
Age (years)	58.00 [52.00, 64.00]	60.00 [50.00, 66.00]	0.094	0.414
BMI (kg/m ²)	23.21 ± 3.12	23.44 ± 3.91	0.063	0.704
EF (%)	60.00 [57.00, 60.00]	60.00 [57.00, 60.00]	0.136	0.712
Preoperative hemoglobin (g/l)	131.00 ± 17.38	134.74 ± 20.56	0.196	0.241
Intravenous fluid (mL)	1000.00 [800.00, 1300.00]	1100.00 [692.50, 1600.00]	0.152	0.795
Intravenous erythrocyte (mL)	0.00 [0.00, 225.00]	0.00 [0.00, 300.00]	0.060	0.746
Autologous blood (mL)	600.00 [250.00, 850.00]	750.00 [500.00, 1000.00]	0.128	0.219
Mechanical blood (mL)	125.00 [0.00, 800.00]	400.00 [0.00, 825.00]	0.026	0.539
Blood loss (mL)	325.00 [300.00, 400.00]	300.00 [300.0, 400.00]	0.089	0.791
Operation time (min)	273.50 [225.00, 327.00]	266.50 [239.00, 332.50]	0.088	0.971
CPB time(min)	119.00 [92.25, 165.25]	118.50 [88.25, 169.50]	0.088	0.887

Abbreviations: ASA, American Society of Anesthesiologists; NYHA, New York Heart Association function class; COPD, chronic obstructive pulmonary disease; CABG, Coronary Artery Bypass Grafting; BMI, body mass index; EF, ejection fraction; CPB, cardiopulmonary bypass.

Table 3 Comparison of Perioperative Indexes Between the Two Groups After PSM

Variables	Group L (N=72)	Group H (N=72)	P-value
Vasoactive drugs, n (%)			<0.001
None	4 (5.56%)	31 (43.06%)	
Yes	68 (94.44%)	41 (56.94%)	
Heart rebound mode, n (%)			0.005
Autonomous	45 (62.50%)	61 (84.72%)	
Defibrillator	27 (37.50%)	11 (15.28%)	
Secondary endotracheal intubation, n (%)			0.620
None	71 (98.61%)	69 (95.83%)	
Yes	1 (1.39%)	3 (4.17%)	
Mortality, n(%)			1.000
None	71 (98.61%)	72 (100.00%)	
Yes	1 (1.39%)	0 (0.00%)	
Postoperative mechanical ventilation time (min)	1641 ± 1436	1741 ± 1666	0.701
Postoperative LOS in hospital (days)	16.3 ± 6.58	16.7 ± 6.53	0.685
LOS in ICU (days)	2.68 ± 1.90	3.22 ± 2.35	0.128

Abbreviation: LOS, length of stay.

drugs. (Table 4). Besides, the univariate regression analysis also showed that the use of sufentanil (OR, 0.301; 95% CI, 0.135, 0.669; P = 0.003), the gender (OR, 2.18; 95% CI, 1.206, 4.63; P = 0.043), preoperative atrial fibrillation (OR, 0.182; 95% CI, 0.052, 0.632; P = 0.007), preoperative smoking history (OR, 3.911; 95% CI, 1.502, 10.183; P = 0.005) and CABG (OR, 3.383; 95% CI, 1.016, 11.267; P = 0.047) were correlated with the heart rebound mode (Table 5).

The variables of P < 0.2 in univariate regression were included in multivariate logistic regression analysis. The results showed that the intraoperative use of sufentanil was an important factor related to the utilization rate of vasoactive drugs (OR, 0.059; 95% CI, 0.017–0.199; P < 0.001) (Table 6). In addition, multivariate logistic regression analysis showed that intraoperative sufentanil infusion (OR, 0.187; 95% CI, 0.071–0.491; P = 0.001), preoperative history of atrial fibrillation (OR, 0.151; 95% CI, 0.037–0.614; P = 0.008), and preoperative smoking history (OR, 3.578; 95% CI, 1.013–12.630; P = 0.048) were also significant factors affecting the success rate of spontaneous heart rebound (Table 7).

Table 4 Results of Univariate Analysis of Variables Associated with Vasoactive Drug Use

	OR (95% CI)	P-value
Sufentanil infusion	0.078 (0.026, 0.236)	<0.001
Gender		
Female	1	
Male	1.049 (0.486, 2.263)	0.903
ASA-status		
II	1	0.606
III	1.027 (0.251, 4.208)	0.970
IV	1.583 (0.349, 7.187)	0.552
NYHA		
I	1	0.217
2	2.1 (0.119, 37.122)	0.613
3	3 (0.180, 49.914)	0.444
4	18 (0.585, 553.586)	0.098

(Continued)

Table 4 (Continued).

	OR (95% CI)	P-value
Preoperative pulmonary infection	1.222 (0.452, 3.308)	0.693
Preoperative hypertension	1.111 (0.500, 2.471)	0.796
Preoperative diabetes mellitus	0.598 (0.206, 1.733)	0.344
Preoperative atrial fibrillation	4.836 (1.384, 16.893)	0.014
Smoker	1.432 (0.448, 4.581)	0.545
COPD	528426350.5 (0.000,)	0.999
Preoperative pulmonary hypertension	1.585 (0.731, 3.435)	0.243
Type of operation		
Valve	I	0.063
CABG	0.204 (0.060, 0.696)	0.011
Combined	2.381 (0.283, 20.063)	0.425
Adult heart disease	1.429 (0.160, 12.772)	0.750
Mixed operation and Others	0.519 (0.209, 1.289)	0.158
Age	1.014 (0.982, 1.047)	0.381
BMI	0.944 (0.848, 1.051)	0.292
EF	0.885 (0.784, 0.998)	0.047
Preoperative hemoglobin	1.005 (0.985, 1.025)	0.621
Intravenous fluid	1.000 (0.999, 1.000)	0.212
Intravenous erythrocyte	1.000 (0.998, 1.002)	0.941
Autologous blood	1.000 (0.999, 1.001)	0.981
Mechanical blood	1.000 (0.999, 1.000)	0.212
Blood loss	0.999 (0.996, 1.002)	0.472
Operation time	1.003 (0.998, 1.008)	0.214
CPB time	1.009 (1.001, 1.017)	0.021

Abbreviations: ASA, American Society of Anesthesiologists; NYHA, New York Heart Association function class; COPD, chronic obstructive pulmonary disease; CABG, Coronary Artery Bypass Grafting; BMI, body mass index; EF, ejection fraction; CPB, cardiopulmonary bypass.

Table 5 Results of Univariate Analysis of Variables Associated with Heart Rebound Mode

	OR (95% CI)	P-value
Sufentanil infusion	0.301 (0.135, 0.669)	0.003
Gender		
Female	I	
Male	2.18 (1.026, 4.63)	0.043
ASA		
II	I	0.557
III	0.808 (0.196, 3.337)	0.768
IV	1.25 (0.29, 5.392)	0.765
NYHA		
I	I	0.450
2	660,869,190.03 (0)	0.999
3	671,036,408.339 (0)	0.999
4	190,053,884.715 (0)	0.999
Preoperative pulmonary infusion	1.147 (0.457, 2.875)	0.770
Preoperative hypertension	1.044 (0.484, 2.253)	0.913
Preoperative diabetes mellitus	1.950 (0.696, 5.466)	0.204

(Continued)

Table 5 (Continued).

	OR (95% CI)	P-value
Preoperative atrial fibrillation	0.182 (0.052, 0.632)	0.007
Smoker	3.911 (1.502, 10.183)	0.005
COPD	0.000 (0.000,)	0.999
Preoperative pulmonary hypertension	0.605 (0.285, 1.285)	0.191
Type of operation		
Valve	I	0.230
CABG	3.383 (1.016, 11.267)	0.047
Combined	0.644 (0.128, 3.238)	0.594
Adult heart disease	0.483 (0.055, 4.264)	0.513
Mixed operation and others	0.859 (0.336, 2.196)	0.751
Age	0.997 (0.966, 1.030)	0.868
BMI	1.027 (0.925, 1.141)	0.615
EF	0.965 (0.888, 1.048)	0.399
Preoperative hemoglobin	1.000 (0.981, 1.020)	0.992
Intravenous fluid	1.000 (1.000, 1.001)	0.628
Intravenous erythrocyte	1.000 (0.999, 1.002)	0.924
Autologous blood	1.000 (0.999, 1.001)	0.990
Mechanical blood	1.000 (0.999, 1.001)	0.707
Blood loss	1.001 (0.999, 1.004)	0.300
Operation time	1.001 (0.997, 1.004)	0.614
CPB time	0.999 (0.994, 1.005)	0.814

Abbreviations: ASA, American Society of Anesthesiologists; NYHA, New York Heart Association function class; COPD, chronic obstructive pulmonary disease; CABG, Coronary Artery Bypass Grafting; BMI, body mass index; EF, ejection fraction; CPB, cardiopulmonary bypass.

Table 6 Results of Multivariate Analysis of Variables Associated with Vasoactive Drug Use

	OR (95% CI)	P-value
Sufentanil infusion	0.059 (0.017, 0.199)	<0.001
NYHA		
I	I	0.571
2	1.647 (0.049, 55.074)	0.780
3	2.072 (0.062, 68.883)	0.684
4	9.605 (0.153, 603.877)	0.284
Preoperative atrial fibrillation		
None	I	
Yes	2.622 (0.599, 11.487)	0.201
Type of operation		
Valve	I	0.370
CABG	0.337 (0.063, 1.789)	0.202
Combined	2.417 (0.233, 25.041)	0.460
Adult heart disease	3.497 (0.280, 43.686)	0.331
Mixed operation and others	0.596 (0.173, 2.057)	0.413
EF	0.908 (0.791, 1.043)	0.173
CPB time	1.005 (0.996, 1.014)	0.268

Abbreviations: NYHA, New York Heart Association function class; CABG, Coronary Artery Bypass Grafting; EF, ejection fraction; CPB, cardiopulmonary bypass.

Discussion

This single-center retrospective cohort study showed that the use of sufentanil during anesthesia was associated with the use of intraoperative vasoactive drugs and the success rate of spontaneous heart rebound. Propensity score matching

Table 7 Results of Multivariate Analysis of Variables Associated with Heart Rebound Mode

	OR (95% CI)	P-value
Sufentanil infusion	0.187 (0.071, 0.491)	0.001
Gender		
Female	1	
Male	1.493 (0.547, 4.077)	0.435
Preoperative atrial fibrillation		
None	1	
Yes	0.151 (0.037, 0.614)	0.008
Smoker		
None	1	
Yes	3.578 (1.013, 12.630)	0.048
Preoperative pulmonary hypertension		
None	1	
Yes	1.082 (0.420, 2.785)	0.871
Type of operation		
Valve	1	0.148
CABG	3.613 (0.789, 16.541)	0.098
Combined	0.536 (0.087, 3.295)	0.501
Adult heart disease	0.255 (0.027, 2.391)	0.232
Mixed operation and others	0.551 (0.185, 1.640)	0.284

Abbreviation: CABG, Coronary Artery Bypass Grafting.

results reinforced the reliability of this analysis. Our results showed that, compared with the low-dose sufentanil group, high-dose sufentanil significantly reduced the use of vasoactive drugs during cardiac surgery under CPB and significantly increased the success rate of spontaneous heart rebound. There was no significant correlation in the duration of mechanical ventilation, postoperative LOS in hospital, and LOS in ICU between the two groups.

At present, there is no consensus on the standard of vasoactive drug utilization in cardiac surgery under CPB.²⁵ There are also significant differences in the use of vasoactive drugs among centers.²⁶ The use of large amounts of vasoactive drugs may be associated with an increased risk of organ dysfunction and increased postoperative in-hospital mortality.^{27,28} In this trial, the utilization rate of vasoactive drugs in the high-dose sufentanil group during surgery was lower than the cohorts in other studies, which was 54.5%. This may be related to the stable hemodynamics during the operation and the low incidence of malignant arrhythmia. Simoni et al²⁹ showed that after the administration of sufentanil, a large peripheral compartment would be formed, resulting in a slow rise of the concentration in the central compartment. Continuous use of sufentanil had less impact on blood pressure and also led to more stable hemodynamics. The use of high-dose sufentanil suppresses the body's stress responses,³⁰ so that the body's oxygen consumption during surgery does not increase with enhanced anesthesia and surgical trauma stimuli,³⁰ at this point, the patient can maintain life with the lowest oxygen consumption and the lowest energy consumption during the operation, obtain the maximum functional reserve, and the utilization rate of vasoactive drugs during the operation is correspondingly lower.

Cardiac resuscitation is a crucial part of the concurrent phase after CPB in patients undergoing cardiac surgery. The ideal cardiac resuscitation is when the ascending aorta is opened and the heart can automatically rebound. If a patient fails to undergo spontaneous heart rebound, increases the number of defibrillations, or experiences arrhythmia after the rebound, it is highly likely to affect hemodynamic stability, leading to an extension of the auxiliary circulation period, or even failure to shut down the CPB machine. The patient's LOS in ICU and hospital will also be prolonged, leading to an increase in complications and a corresponding increase in mortality. Poor myocardial protection during operation is a common cause of difficulty in cardiac resuscitation. In this study, the success rate of spontaneous heart rebound in the high-dose sufentanil group (84.72%) was significantly higher than that in the low-dose sufentanil group (62.5%). This may be related to the mechanism that sufentanil can simultaneously activate μ , κ , and δ opioid receptors. Related studies have shown that κ and δ opioid receptors, alone³¹ or

together,³² are involved in reducing myocardial ischemia-reperfusion injury. Sufentanil binds to opioid receptors on the coronary endothelium, activates the cellular pathway, reduces the production of oxygen free radicals, and accordingly reduces the myocardial damage caused by oxidative stress. To a certain extent, the use of high-dose sufentanil can avoid irreversible myocardial injury and necrosis, improve myocardial energy supply, and maintain electrophysiological stability before the opening of the ascending aorta, which is beneficial to the recovery of cardiac function and smooth heart rebound of patients. In addition, similar to previous studies,^{33–35} this study confirmed that the history of preoperative smoking and atrial fibrillation were significantly associated with spontaneous heart rebound during CPB. However, multivariate logistics regression analysis did not show a correlation between spontaneous rebound success and other known risk factors, which may be due to the small sample size of this study, or because the medical data of patients undergoing cardiac surgery under CPB were collected and analyzed in only one tertiary medical center. The anesthetic and surgical conditions of all patients are generally similar, so it is difficult to reveal the statistically significant correlation between these variables and the success rate of spontaneous heart rebound.

There were wide differences in the duration of mechanical ventilation after cardiac surgery with CPB.³⁶ This large range may be related to different patient populations, surgical procedures, and anesthesia conditions.^{37,38} The duration of postoperative mechanical ventilation of participants in this trial was 1899.87 minutes, which was longer than in cohorts from other studies.³⁹ This may be related to the longer intraoperative CPB time (144.75 min), which has been shown in relevant studies to be a major cause of early extubation failure in patients undergoing cardiac surgery.⁴⁰ According to previous studies, the duration of postoperative mechanical ventilation was associated with preoperative comorbidities and increased with patient age.^{37,38} Prolonged operative time and excessive intraoperative blood loss are also known risk factors for prolonged postoperative mechanical ventilation.⁴¹ The mean age of the patients included in this trial was significantly older than the cohort from other studies. Compared with 95.6% of the patients in this trial, only 50% of the patients in cohorts from other studies had an ASA grade III or above.

The traditional view is that heavy use of opioids in cardiovascular surgery will lead to slow postoperative awakening as well as prolonged mechanical ventilation and LOS in ICU, which is not conducive to postoperative rehabilitation.^{11,16,42} A multicenter Cochrane Trial⁴³ reported that the use of high-dose opioid anesthesia was associated with prolonged extubation time (3–10.5 h) and LOS in ICU (0.4–8.7 h). However, in this trial, the use of high-dose sufentanil did not significantly extend the duration of postoperative mechanical ventilation in the included patients ($P=0.611$). Given the differences in patient management by year and the high heterogeneity reported in this Cochrane report, such differences were not unacceptable. In addition, the study of Michael⁴⁴ et al also reached a similar conclusion, that is, there was no difference in extubation time and LOS in hospital between the low-dose opioid group and the high-dose opioid group. The mechanisms involved, although unclear, may be related to the favorable anti-inflammatory effects of sufentanil. The use of high-dose sufentanil is effective in preventing acute lung injury and microatelectasis caused by inflammatory cascade after cardiac surgery, thereby preventing the occurrence of postoperative hypoxia, which reduces the incidence of prolonged postoperative mechanical ventilation and the LOS in ICU after cardiac surgery. As a potent opioid analgesic drug, sufentanil has an active metabolite produced in clinical use, which has a further residual effect, contributing to the reduction of postoperative gastrointestinal reactions and the LOS in ICU.

The limitations of this study are as follows: First, this retrospective study has more potential confounding factors than randomized controlled trials. Additionally, some patients were excluded by lack of data. Therefore, there may be selection bias in the samples. Second, the use rate of vasoactive drugs and the rate of spontaneous heart rebound were selected as hemodynamic indicators in this study due to the hemodynamic particularity of cardiac surgery under cardiopulmonary bypass, which can only indirectly reflect the stability of cardiovascular response. Third, the surgical and anesthetic conditions were broadly similar among all patients from a single-center study, making it difficult to reveal statistical associations between the different variables. Finally, the conclusions of this study needs to be further verified through a more comprehensive large-scale, multi-center prospective study.

In summary, the dose of sufentanil during operation was significantly correlated with the utilization rate of vasoactive drugs and the success rate of spontaneous heart rebound among patients who received cardiac surgery under CPB. The high-dose sufentanil had a better intraoperative cardiovascular response than the low-dose sufentanil, but there was no significant difference on the quality of early postoperative recovery.

Data Sharing Statement

All data generated or analyzed during this study are included in the article. Further inquiries about the datasets can be directed to the corresponding author on reasonable request.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Disclosure

The authors report no conflicts of interests in this work.

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