

## Original Article

# Comparison between nitroglycerin and remifentanil in acute hypervolemic hemodilution combined with controlled hypotension during intracranial aneurysm surgery

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**Abstract:** Allogenic transfusion has long been considered to be a relatively safe and extremely effective blood transfusion treatment. However, acute hypervolemic hemodilution (AHH) combined with the remifentanil-induced controlled hypotension (CH) have rarely been examined. Herein, 40 intracranial aneurysm surgery patients were randomly divided into nitroglycerin group (A group, n=20) and remifentanil group (B group, n=20). During intracranial aneurysm surgery, MAP, HR, Hb, and Hct were recorded.  $SjvO_2$ ,  $PjvO_2$ ,  $SaO_2$ ,  $PaO_2$  were measured, and  $CaO_2$ ,  $Da-jvO_2$ ,  $CjvO_2$ ,  $CERO_2$ , VADL were calculated. In addition, The venous blood samples were collected for determining PT, TT, APTT, FBG, VIII, VWF and electrolytes. The results show that HR in nitroglycerin group dramatically accelerated and HR in remifentanil group slowed at 30 minutes after hypotension and 5 minutes after aneurysm occlusion ( $P<0.01$ ) after hypotension. Compared with A group, the  $SjvO_2$  and  $CjvO_2$  of B group increased significantly and the  $Da-jvO_2$  and  $CERO_2$  decreased significantly at  $T_3$ ,  $T_4$ . In addition, There were no significant differences between after AHH and before AHH in two groups ( $P>0.05$ ) on TT, PT, APTT, FIB, VIII, VWF,  $Na^+$ ,  $Cl^-$ ,  $K^+$ ,  $Ca^{2+}$ . These results suggest that AHH combined with remifentanil-based CH significantly lowered cerebral metabolic rate of oxygen and had effects on blood coagulation without clinical hemorrhagic signs increased and had important clinical significance for blood conservation.

**Keywords:** Acute hypervolemic hemodilution, remifentanil, controlled hypotension, intracranial aneurysm surgery

## Introduction

Since surgical operation appeared, the problem of bleeding and blood transfusion in surgery has been tightly concerned by doctors and patients. Allogenic transfusion has long been considered to be a relatively safe and extremely effective treatment, especially in emergency [1]. However, more and more patients are recently terrified about allogenic transfusion due to its life-threatening adverse reactions and effects. In recent years, researchers are trying to apply new, effective blood conservations to control blood loss and decrease (or avoid) allogenic transfusion in surgery. Among various methods to conserve blood, acute hemodilution, clinically divided into acute normovolemic hemodilution (ANH) and acute hypervolemic hemodilution (AHH), attracts huge attention [2-4].

Studies on ANH are growing, but its defects should not be ignored, such as time and supplies consuming. What's more, complex operation and possibility in blood contamination further limit the clinical application of ANH. Compared with autologous blood-collected ANH, AHH characterized by less or even no allogenic transfusion, seems more safe and acceptable in surgery [5, 6]. AHH is a procedure that a certain amount of crystal liquid cargo or colloidal fluid rapidly perfused in a short time (30 to 35 minutes) under a successful preoperative anesthesia, which ultimately leads to rapid dilation of blood volume (20 to 30%) and low hematocrit level (28 to 32%) [7]. Thus, not only can AHH reduce the loss of visible component in blood during surgery, but it can also increase hemorrhagic tolerance of patients. In addition, AHH is time and labor saving, low-cost

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**Table 1.** General information in two groups (n=20)

Groups	Group A	Group B
Gender (male/female)	14/6	15/5
Age (years)	37.3±2.5	35.4±3.5
Weight (Kg)	54.3±9.5	56.3±7.6
ASA class (I/II)	11/9	9/11
Hb before operation (g/L)	130±10	132±11
Hct before operation (%)	43±3	42±5
Albumin before operation(g/L)	37±3	36±4
Blood Loss (mL)	734.3±78.5	710.9±75.9
Duration of operation (min)	235.1±5.17	236.9±5.05

and easy-popularized, which attracts more and more attention.

Recently, further study of ANH brings a fascinating improvement-AHH combined with controlled hypotension (CH). It can modestly dilate vessel capacity and maintain a normal central venous pressure (CVP). More importantly, it can avoid dangerous clinical symptom, such as pneumoedema, heart failure, etc [8]. Under general anesthesia, methods to improve low cerebral metabolic rate of oxygen and weak cerebral auto-regulation are urgently needed. Application of AHH makes blood capacity exceed the normality, which ultimately balances cerebral oxygen delivery and consumption through regulating blood delivery according to the cerebral function and metabolism, and orchestrating cerebral blood flow and metabolism [9]. At present, the study of AHH combined with nitroglycerin-induced CH is more than combined with the Remifentanil-induced CH [10]. Remifentanil is a new type of potent, ultra-short acting  $\mu$ -opioid receptor agonist that has gained growing popularity for its moderate anti-hypertensive effect and avoidance of reflective heart rate (HR) acceleration and rebound hypertension [11]. Herein, we reported that the effect of acute hypervolemic hemodilution (AHH) combined with the remifentanil-induced controlled hypotension (CH) on hemodynamics, cerebral oxygen metabolism and coagulation in 40 patients undergoing intracranial aneurysm surgery.

### Patients and methods

#### *Patient enrollment*

A total of 60 patients scheduled to have encephalic aneurysm surgery were selected in our study. The inclusion criteria were as follows:

Hunt-Hess status I-II, American Society of Anesthesiologists (ASA) status I-II, aged 30-55 years, weighting 42-47 kg, normal function of liver, kidney and coagulation, no severe pulmonary or cardiovascular diseases, preoperative hematocrit (HCT) 35-45%, hemoglobin (HB)  $\geq 100$  g/L, albumin 35-45 g/L. Patients were randomly divided into nitroglycerin group (A group) and remifentanil group (B group).

#### *Preparation before operation*

Patients were intramuscular injected 0.5 mg Penehyclidine Hydrochloride 30 minutes before operation. Anesthesia in two groups was induced with intravenous administration of 0.05 mg/kg midazolam, 3-4  $\mu$ g/kg fentanyl, 1mg/kg atracurium and 1.5-2 mg/kg propofol. After tracheal intubation, anesthesia was maintained with 3-6 mg/kg propofol and 0.5-0.7 atracurium by micro pump. Intermittent, intravenous fentanyl was used to maintain analgesia in A group. 6-10  $\mu$ g/kg $\cdot$ h (12-30  $\mu$ g/kg $\cdot$ h in CH) remifentanil was intravenously administered by micro pump to maintain analgesia. In order to avoid hyperalgesia response caused by remifentanil withdrawal in B group, 0.1-0.2 mg fentanyl was intravenously administered 30 minutes before the end of operation. Catheterization on radial artery was conducted after anesthesia induction to continuously monitor arterial BP. To collect blood for analysis, double-lumen tube was intubated and in the right internal jugular vein, and catheter was intubated 12-15 cm in the left internal jugular vein near cranium (until the resistance was sensed) to assure the tip of catheter reached the level of internal jugular bulb (surface projection in the earlobe).

#### *Acute hypervolemic hemodilution*

After each patient arrived in the operating theatre, 6-8 ml/kg compound sodium lactate was transfused to compensate the loss of body fluid caused by deprivation of water and food. Dura mater was cut after transfusion of 15-20 ml/kg $\cdot$ h 6% hydroxyethyl starch (HES) before operation. HCT was monitored at 30 minutes in AHH. Once it was stable at 25-32%, HCT was maintained with normal saline at a low transfusion rate. To maintain HCT $>25\%$ , allogeneic transfusion was implemented when the Hb $<80$  g/L and HCT $<25\%$ .

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**Table 2.** The hemodynamics and blood dilution degrees of two groups

Index	Group	n	T <sub>0</sub>	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>
MAP (mmHg)	A	20	82.8±16.2	84.6±17.5	85.1±10.5	62.3±7.9*	63.4±8.7*
	B	20	88.6±14.3	89.1±16.7	86.9±9.7	64.3±8.8*	63.5±9.4*
HR (times/min)	A	20	79.6±9.4	81.0±11.5	80.5±9.7	99.4±11.6*	98.2±10.3*
	B	20	81.8±10.2	79.4±9.3	79.8±9.5	62.4±5.6* <sup>▲</sup>	60.7±5.3* <sup>▲</sup>
Hb (g/L)	A	20	118.7±14.2	92.0±12.5 <sup>#</sup>	95.1±12.8 <sup>#</sup>	94.0±15.6 <sup>#</sup>	93.8±14.8 <sup>#</sup>
	B	20	121.8±13.6	93.4±12.0 <sup>#</sup>	94.8±14.4 <sup>#</sup>	93.2±16.1 <sup>#</sup>	92.7±17.3 <sup>#</sup>
Hct (%)	A	20	38.9±6.8	30.8±5.4 <sup>#</sup>	30.8±4.9 <sup>#</sup>	30.8±7.3 <sup>#</sup>	29.0±5.4 <sup>#</sup>
	B	20	39.4±7.2	29.3±4.6 <sup>#</sup>	30.3±5.5 <sup>#</sup>	30.9±7.4 <sup>#</sup>	29.8±6.2 <sup>#</sup>

MAP: mean arterial pressure; HR: heart rate; Hb: hemoglobin; Hct: hematocrit. Data are expressed as mean ± S.D., n=20. Significant differences compared with control group. <sup>#</sup>P<0.01, compared with the mean values at T<sub>0</sub>; \*P<0.01, compared with the mean values at T<sub>2</sub>; <sup>▲</sup>P<0.01, compared with the mean values in A group.

**Table 3.** The blood gas analysis index undergoing AHH of patients in two groups

Index	Group	n	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>
PaO <sub>2</sub> (mmHg)	A	20	518.4±48.7	508.5±61.2	511.8±53.6
	B	20	520.4±43.0	495.9±58.4	507.7±47.6
CaO <sub>2</sub> (ml/L)	A	20	130.9±17.3	128.0±19.3	127.7±18.9
	B	20	130.8±18.1	129.4±20.4	128.2±17.9
PjvO <sub>2</sub> (mmHg)	A	20	36.5±14.9	41.7±12.1	39.2±9.5
	B	20	35.9±12.0	39.7±14.8	40.6±11.5
SjvO <sub>2</sub> (%)	A	20	67.8±9.3	68.6±9.7	69.5±8.2
	B	20	67.8±11.3	84.6±9.3* <sup>#</sup>	83.9±10.2* <sup>#</sup>
CjvO <sub>2</sub> (ml/L)	A	20	87.8±16.5	87.7±17.2	86.6±16.4
	B	20	87.5±17.9	107.3±20.5* <sup>#</sup>	105.9±22.4* <sup>#</sup>
VADL (mmol/L)	A	20	0.15±0.07	0.14±0.06	0.18±0.05
	B	20	0.15±0.06	0.14±0.07	0.16±0.04
Da-jvO <sub>2</sub> (ml/L)	A	20	41.6±11.2	40.8±12.4	39.6±10.7
	B	20	42.1±12.3	21.0±8.5* <sup>#</sup>	21.8±9.8* <sup>#</sup>
CERO <sub>2</sub> (%)	A	20	32.9±8.0	32.2±7.1	31.5±7.6
	B	20	33.2±8.9	16.2±6.2* <sup>#</sup>	17.1±7.1* <sup>#</sup>

PaO<sub>2</sub>: partial pressure of oxygen; CaO<sub>2</sub>: arterial oxygen content; PjvO<sub>2</sub>: jugular bulb venous oxygen tension; SjvO<sub>2</sub>: jugular bulb oxygen saturation; CjvO<sub>2</sub>: jugular venous oxygen content; VADL: venous-arterial difference of lactate; Da-jvO<sub>2</sub>: arteriovenous O<sub>2</sub> content difference; CERO<sub>2</sub>: cerebral extraction ratio for oxygen. Data are expressed as mean ± SD., n=20. Significant differences compared with control group. \*P<0.01, compared with the mean values at T<sub>2</sub>; <sup>#</sup>P<0.01, compared with the mean values in A group.

### Controlled hypotension

250 ml mannitol (40%) was transfused before craniotomy in two groups. After the cut on dura mater, CH was implemented during aneurysm isolation and clipping. 1-5 µg/kg\*min nitroglycerin was pumped in patients from A group, and 12-30 µg/kg\*h remifentanil was pumped in patients from B group. The pumped speed of c was slowed when mean artery pressure (MAP)

reached 65 mmHg. Antihypertensive effect of nitroglycerin and remifentanil was seldom unsatisfied, except for those who associated with other antihypertensive drugs. CH was stopped 10 minutes after aneurysm clipping.

### Measuring parameters

Dash 2000 monitor was intra-operative used to continuously monitor patients' systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, HR, electrocardiogram (EGG), Saturation of Peripheral Oxygen (SpO<sub>2</sub>) and invasive radial artery blood pressure (IBP). MAP, HR, Hb and HCT were recorded in two groups at five different time points: before AHH (T<sub>0</sub>), after AHH (T<sub>1</sub>), before depressurization (T<sub>2</sub>), 30 minutes after depressurization (T<sub>3</sub>) and 5 minutes after aneurysm clipping (T<sub>4</sub>). For analysis, blood from internal jugular bulb and radial arterial was collected at T<sub>2</sub>-T<sub>4</sub>. After blood collection, jugular bulb oxygen saturation (SjvO<sub>2</sub>), jugular bulb venous oxygen tension (PjvO<sub>2</sub>), arterial oxygen saturation (SaO<sub>2</sub>), partial pressure of oxygen in arterial blood (PaO<sub>2</sub>), Hb and HCT were all measured. Meanwhile, arterial oxygen content (CaO<sub>2</sub>), arteriovenous O<sub>2</sub> content difference (Da-jvO<sub>2</sub>), jugular venous oxygen content (CjvO<sub>2</sub>), cerebral extraction ratio for oxygen (CERO<sub>2</sub>) and venous-arterial difference of lac-

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**Table 4.** The changes of coagulation function of patient in two groups

Index	Group	n	t <sub>1</sub>	t <sub>2</sub>	t <sub>3</sub>	t <sub>4</sub>
PT (s)	A	20	13.7±1.5	15.0±1.9 <sup>#</sup>	14.8±1.6 <sup>#</sup>	14.6±1.7 <sup>#</sup>
	B	20	13.9±1.3	15.1±1.6 <sup>#</sup>	14.4±1.2 <sup>#</sup>	14.9±1.3 <sup>#</sup>
TT (s)	A	20	10.4±0.9	10.5±1.4	10.8±1.4	9.9±1.1
	B	20	10.7±1.4	10.8±2.4	10.4±1.1	9.7±1.2
APTT (s)	A	20	27.2±2.1	37.2±5.8 <sup>#</sup>	35.6±3.6 <sup>#</sup>	34.8±4.8 <sup>#</sup>
	B	20	27.4±1.0	37.8±4.4 <sup>#</sup>	35.2±3.1 <sup>#</sup>	35.1±5.3 <sup>#</sup>
FIB (g/L)	A	20	2.87±0.41	2.50±0.49 <sup>#</sup>	2.21±0.73 <sup>#</sup>	2.23±0.54 <sup>#</sup>
	B	20	2.84±0.31	2.48±0.25 <sup>#</sup>	2.25±0.53 <sup>#</sup>	2.17±0.44 <sup>#</sup>
VIII (%)	A	20	100.7±10.5	93.2±8.9 <sup>#</sup>	90.8±6.1 <sup>#</sup>	94.4±9.7 <sup>#</sup>
	B	20	103.9±9.3	95.1±8.6 <sup>#</sup>	90.4±7.2 <sup>#</sup>	94.9±8.3 <sup>#</sup>
vWF (%)	A	20	97.7±4.5	94.2±5.9 <sup>#</sup>	94.0±6.1 <sup>#</sup>	92.4±7.7 <sup>#</sup>
	B	20	96.8±5.4	93.7±4.8 <sup>#</sup>	93.0±5.1 <sup>#</sup>	92.0±7.3 <sup>#</sup>

PT: prothrombin time; TT: thrombin time; APTT: partial thromboplastin time; FIB: fibrinogen; vWF: von Willebrand factor. Data are expressed as mean ± SD., n=20. Significant differences compared with control group. <sup>#</sup>P<0.01, compared with the mean values at t<sub>1</sub>.

**Table 5.** The changes of electrolytes in two groups

Index	Group	n	t <sub>1</sub>	t <sub>2</sub>	t <sub>3</sub>	t <sub>4</sub>
Na <sup>+</sup> (mmol/L)	A	20	139.7±2.2	142.1±3.3	140.2±2.3	140.9±3.2
	B	20	140.9±1.8	143.0±2.9	139.5±2.5	140.2±3.4
Cl <sup>-</sup> (mmol/L)	A	20	105.8±3.1	117.2±2.2	108.7±1.6	109.1±1.4
	B	20	106.9±1.9	116.6±1.7	109.1±1.6	111.1±2.7
K <sup>+</sup> (mmol/L)	A	20	4.2±0.5	4.1±0.3	4.0±0.2	4.0±0.4
	B	20	4.1±0.4	4.0±0.3	4.1±0.3	4.1±0.3
Ca <sup>2+</sup> (mmol/L)	A	20	1.26±0.01	1.21±0.02	1.22±0.03	1.22±0.04
	B	20	1.25±0.01	1.20±0.01	1.22±0.02	1.22±0.02

tate (VADL) were calculated based on following formulas:  $CaO_2 = Hb \times 1.36 \times SaO_2 + PaO_2 \times 0.0031$ ,  $CjvO_2 = Hb \times 1.36 \times SjvO_2 + PjvO_2 \times 0.0031$ ,  $Da-jvO_2 = CaO_2 - CjvO_2$ ,  $CERO_2 = Da-jvO_2 / CaO_2$ .

### Coagulation and electrolytes parameters

The change of prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (APTT), fibrinogen (FIB), VIII, vWF and electrolytes were measured at four different time points: before AHH (t<sub>1</sub>), at the end of AHH (t<sub>2</sub>), 60 minutes after AHHD (t<sub>3</sub>), 120 minutes after AHH (t<sub>4</sub>).

### Statistical analysis

All data are expressed as mean ± SD. Statistical differences among groups were analyzed by

the one-way analysis of variance (ANOVA) and two-tailed Student's t-test. A value of P<0.05 was considered significant.

### Results

#### *The hemodynamics and blood dilution degrees of patients with intracranial aneurysm surgery*

General data including age, gender, weight, intraoperative blood loss, ASA, Hct, Hb, albumin and duration of operation were not significantly different between the two groups (P>0.05) (Table 1).

Table 2 shows the rheological variables at different times for the two groups. Within two groups, after AHH with 6% HES, HCT decreased 30% and Hb decreased to 93 g/L, MAP and HR had no differences, and the Hb and Hct decreased significantly at T<sub>1</sub>, T<sub>2</sub> compared with T<sub>0</sub> (P<0.01), which suggested a successful hemodilution. After hypotension, HR in nitroglycerin group (A group) dramatically accelerated and HR in remifentanil group (B group) slowed at 30 minutes after hypotension and 5 minutes after aneurysm occlusion.

#### *The blood gas analysis index undergoing AHH of patients with intracranial aneurysm surgery*

As shown in Table 3, compared with A group, the SjvO<sub>2</sub> and CjvO<sub>2</sub> of B group increased significantly and the Da-jvO<sub>2</sub> and CERO<sub>2</sub> of B group decreased significantly at T<sub>3</sub>, T<sub>4</sub>. There were no significant intra-group or intergroup difference among two group on PaO<sub>2</sub>, CaO<sub>2</sub>, PjvO<sub>2</sub>, VADL (all P>0.05).

#### *Coagulation function of patient in two groups*

As shown in Table 4, there were no significant intra-group differences on coagulation function of patient in two groups. PT, APTT, FIB, VIII and

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VWF were significantly changed in two groups (all  $P < 0.01$ ), and they did not exceed normal range and the phenomenon of clinical operation blood oozing and bleeding difficult were not obvious (**Table 4**).

### *Electrolytes of patient in two groups*

As shown in **Table 5**, there were no significant intra-group differences on the concentration of  $\text{Na}^+$ ,  $\text{Cl}^-$ ,  $\text{K}^+$  and  $\text{Ca}^{2+}$  of patient in two groups. But, After AHHD,  $\text{Ca}^{2+}$  decreased in group A and group B, which attentions should be taken and supplement of  $\text{Ca}^{2+}$  is necessarily given.

### **Discussion**

CH is famous for its ability to control blood loss, improve environment of operative field, decrease aneurysmal transmural pressure (TMP) and avoid the rupture of aneurysm during separate. However, its prolonged application may lead to cerebrovascular insufficiency and hypoxia [12]. Stable TMP, maintained by preoperative AHH, improved the dehydrated situation that resulted from fasting, diuretics and dehydration. What's more, stable intraoperative hemodynamics after AHH effectively controlled the risk of ruptured aneurysm or cerebral ischemia that caused by drastic fluctuation in hemodynamics. Furthermore, CH improved the safety by improving reserve capacity and eliminating its infused influence on cerebra [13]. As our results showed, after AHH with 6% HES, HCT decreased 30% and Hb decreased to 93 g/L, suggesting a successful hemodilution.

Many kinds of clinical drugs have been applied to CH in intracranial aneurysm surgery. However, adverse drug reactions should not be ignored, such as myocardial depression, cardiac arrhythmia, faster HR, cyanide poisoning, delayed recovery, etc. Herein, we conducted CH with remifentanil and nitroglycerin. Under decomposition and transformation in vivo, nitroglycerin becomes vasodilator by releasing NO, which accelerates reflective HR. But it could also be harm when it is prolonged used, as it easily leads to rapid vascular tolerance, rebound hypertension and potential cyanide poisoning. Tachycardia is serious damage to the cardiovascular system, because it could increase myocardial oxygen consumption and disturb oxygen supply [14]. Consistent with this,

our study showed that HR in nitroglycerin group dramatically accelerated at 30 minutes after hypotension. As a potent, ultra-short acting  $\mu$ -opioid receptor agonist, remifentanil has moderate advantage for anti-hypertension. The possible anti-hypertensive mechanisms of remifentanil are as follows [15-17]: (1) suppression on autonomic or central nervous system. (2) Inhibition on catecholamine release during operation, especially on adrenaline. (3) Dilation on blood vessels through endothelial-dependent release of prostacyclin and nitric oxide (NO); (4) endothelial-independent dilation on blood vessels through voltage-dependent calcium channel. As our results showed, anti-hypertensive effect in remifentanil group was significant. Meanwhile, HR slowed at 30 minutes after hypotension and 5 minutes after aneurysm occlusion. The results may possibly associate with excited vagus nerve and inhibited sinus node that regulated by opioid receptor agonist.

Assessment of cerebral oxygen metabolism and balance is the authoritative standard to determine the safety of AHH combined with CH. According to Fick theory,  $\text{SjvO}_2$  and arteriovenous  $\text{O}_2$  content difference ( $\text{Da-jvO}_2$ ) may reflect the relationship between cerebral blood flow and cerebral oxygen consumption- that is oxygen balance. Therefore, collect blood from jugular bulb to detect  $\text{SjvO}_2$  and calculate  $\text{Da-jvO}_2$  is very important to accurately assess the whole-brain blood flow and metabolism [18].  $\text{CERO}_2$  (normally 23%-32%) can reflect organic respiratory situation and organic perfusion, which is tightly relative to microcirculation perfusion. Thus, oxygen supply and consumption in brain tissue can be reflected by  $\text{CERO}_2$  and VADL respectively. Internal jugular vein blood, directly reflex from brain tissue, can be collected with retrograde catheterization in internal jugular vein. And VADL of internal jugular vein blood directly reflects the net lactic acid production in brain tissue [19]. The value of VADL is normally  $(0.19 \pm 0.10)$  mmol/L. Once exceed  $(0.19 \pm 0.10)$  mmol/L, VADL indicates a relative lack of oxygen supply and increased anaerobic metabolism in brain. In the current study, we evaluated the cerebral oxygen metabolism in patients with aneurysm by monitoring  $\text{SjvO}_2$ ,  $\text{CERO}_2$ ,  $\text{Da-jvO}_2$ ,  $\text{PjvO}_2$  and  $\text{CjvO}_2$ . In remifentanil-based CH group,  $\text{SjvO}_2$  and  $\text{CjvO}_2$  significantly increased, but  $\text{Da-jvO}_2$  and  $\text{CERO}_2$  significantly decreased. However,  $\text{SjvO}_2$ ,  $\text{CERO}_2$ ,  $\text{CjvO}_2$  and



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Da-jvO<sub>2</sub> did not change significantly in nitroglycerin group-induced CH group. Therefore, these results suggested that CH with remifentanil effectively weakened oxygen metabolism and enhanced hypoxia tolerance in brain tissue. Meanwhile, remifentanil weakened brain electrical activity, dose-dependently dilated blood vessels, increased cerebral blood flow and ameliorated cerebral vasospasm, which ultimately maintained an excellent balance between blood flow and metabolism in brain. AHH has been reported to decrease cerebral oxygen metabolism. The relatively stable CERO<sub>2</sub> in nitroglycerin group possibly associated with increased oxygen consumption that induced by high HR after CH with nitroglycerin, which consistent with the report of Fukusaki [20]. VADL in two groups did not change dramatically (within normal range), indicating that AHH combined with CH (remifentanil-induced or nitroglycerin-induced) properly regulated cerebral oxygenation without organic hypoxia and organic anaerobic glycolysis.

Normally, coagulation and anti-coagulation system, associated with clotting factors, platelets and fibrinolytic system, are counter-balanced to maintain homeostasis. Any abnormalities in two systems may lead to coagulation dysfunction. Herein, we detected the change of PT, TT, APTT, FIB, VIII, vWF. PT was an indicator of the extrinsic coagulation and easily affected by coagulation factors (II, V and X) [21]. Under AHHD, PT of B groups increased (<3 s compared to control), but still within normal range, suggesting that AHH has no effect on extrinsic coagulation. Thrombin formation is indispensable in both endogenous and exogenous coagulation. Thrombin accelerates the process of coagulation through positive feedback once it is lightly formed, which can be reflected by TT [21]. Under AHH, TT of B groups without changes suggesting that AHH has no effect on the second stage of coagulation. APTT was an indicator to reflect endogenous coagulation factor and was tightly relative to the concentration of coagulation factors (VIII, IX, X, XI) [21]. Under AHH, APTT of B group increased (<10 s compared to control) and exceed normal range, but still without significant blood oozing from operative field and difficulty in hemostasis. Martin [22] reported that decreased coagulation factors (III, IX, X, XI, XII) caused by transient hemodilution led to increased APTT. DeJonge [23] reported that HES influenced coagulation by decreasing factor III and VWF. Treib [24] thought

that HES (130/0.4) could decrease VWF complex to prolonged APTT. Fibrins from degraded FIB are inclined to form a stable clot, which ultimately leads to hemostasis. Our results showed that FIB decreased after AHH, but still within normal range. And the differences of FIB were statistically significant.

In conclusion, the study of AHH combined with remifentanil-based CH applied to intracranial aneurysm surgery was conducted. AHH effectively prevented and ameliorated cerebral vasospasm, and improved reduced tissue perfusion induced by CH. Meanwhile, high cardiac load evoked by AHH could be lightened by CH. Thus, AHH combined with CH was excellent in maintaining hemodynamics in a relatively stable condition. In addition, AHH combined with remifentanil-induced CH significantly lowered cerebral metabolic rate of oxygen and had no negative effect on blood coagulation and electrolytes, which proved that AHH combined with remifentanil-based CH was superior to AHH combined with nitroglycerin-induced CH and had important clinical significance for blood conservation.

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### Disclosure of conflict of interest

None.

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