

# Efficacy of inhalational sevoflurane anesthesia induction on inhibiting the stress response to endotracheal intubation in children with congenital heart disease

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**Abstract.** – **OBJECTIVE:** To investigate the efficacy of inhalational sevoflurane anesthesia induction on inhibiting the stress response to endotracheal intubation in pediatric patients with congenital heart disease (CHD).

**PATIENTS AND METHODS:** Forty ASA physical status I/II pediatric patients scheduled for interatrial septal defect repair or interatrial septal defect repair, were randomly divided into two groups (20 each): intravenous induction group (Group C) and inhalational sevoflurane anesthesia induction group (Group D). In group C, anesthesia was induced with midazolam, pipecuronium bromide and fentanyl, and the children were examined by radial artery monitoring after the consciousness extinction. Also, they were endotracheally intubated after muscle relaxation. In group D, anesthesia was induced with inhalation of 8% sevoflurane and 6 L/min oxygen, and the children were examined by radial artery monitoring after the consciousness extinction and were endotracheally intubated 4 min later. Before anesthesia induction (T<sub>0</sub>), consciousness extinction (T<sub>1</sub>), endotracheal intubation (T<sub>2</sub>), endotracheal intubation (T<sub>3</sub>), and after endotracheal intubation (T<sub>4</sub>), 1 and 3 min after intratracheal intubation (T<sub>5,6</sub>), HR and bispectral index (BIS) were monitored. The MAP of T<sub>2</sub>-T<sub>6</sub> points was recorded. Ulnar vein blood samples were taken for determination of Endothelin (ET) and Thromboxane A<sub>2</sub>(TXA<sub>2</sub>) in the points of consciousness extinction, and 5 and 10 min after endotracheal.

**RESULTS:** All the children were well examined by endotracheal intubation. Compared with the baseline value at T<sub>0</sub>, there was no significant difference of HR in group D, but the HR of group C was decreased at T<sub>2</sub>, T<sub>3</sub>, T<sub>4</sub> and T<sub>6</sub>. The BIS of the two groups were decreased at T<sub>1</sub>-T<sub>6</sub> ( $p < 0.05$ ). Compared with the values at T<sub>2</sub>, they were increased at T<sub>5</sub> and T<sub>6</sub> in group C, and increased at T<sub>6</sub> in group D ( $p < 0.05$ ). Compared with group

C, the MAP of group D was decreased at T<sub>5</sub>, and the BIS of the two groups was decreased at T<sub>2</sub>-T<sub>6</sub> ( $p < 0.05$ ). There were no significant differences of ET and TXA<sub>2</sub> between groups.

**CONCLUSIONS:** It is well inhibited the endotracheal intubation stress response in children with congenital heart diseases using sevoflurane inhalational anesthesia induction.

## Key Words

Congenital heart disease, Child, Anesthetics, Inhalation, Intubation, Endotracheal, Stress.

## Introduction

Sevoflurane, a non-irritating inhalational anesthetic agent with less interference to respiration, good senses of smell, and rapid onset of unconsciousness, is generally used for inhalation induction of anesthesia<sup>1,2</sup>. Also, sevoflurane is widely used to anesthesia induction of tracheal intubation without muscle relaxants, because of the strong controllability in difficult airway and no need establishment of intravenous access<sup>3,4</sup>. It has been confirmed that the stress response to tracheal intubation in one of the main disadvantages during inhalation induction and strong stimulation induced by tracheal intubation, may cause some intense effects in circulation, endocrine, nervous, and other systems. Hemodynamic changes have been proven to be the direct and rapid response to tracheal intubation. Stress hormones, such as endothelin (ET) and thromboxane A<sub>2</sub> (TXA<sub>2</sub>) liberated in response to intubation stimulus, participate in stress response<sup>5</sup>. Due to the special physiological defect of heart in children wi-

th congenital heart disease, the accurate control of anesthesia depth plays an important role in carrying out endotracheal intubation and reducing complications<sup>6,7</sup>. Previous studies<sup>8-10</sup> have provided that sevoflurane is widely used in minor surgeries, such as tracheal foreign body removal, tonsillectomy, and magnetic resonance imaging examination, which have no requirement for endotracheal intubation. In some surgeries concerning endotracheal intubation, sevoflurane is commonly used in intubation surgery for loss of consciousness. However, sevoflurane combined with other narcotic drugs for tracheal intubation has been described; previous studies<sup>11,12</sup> analyzed sevoflurane combining with narcotic sedative drugs (propofol), narcotic analgesics (fentanyl) or muscle relaxant. Moreover, it was reported that proseal laryngeal mask airway insertion was completed successfully by sevoflurane induction<sup>9</sup>. Sevoflurane possesses multiple properties including muscle relaxant efficacy and enhancing muscle relaxants of other drugs; therefore, we speculated that sevoflurane might decrease the target concentration of muscle relaxant needed to perform tracheal intubation in children<sup>11,13</sup>. However, whether only sevoflurane anesthesia induction inhibits the stress response to endotracheal intubation remains unclear. Therefore, we designed a study to determine the effect of only sevoflurane anesthesia induction on inhibiting the stress response to endotracheal intubation.

## Patients and Methods

### Patients

The protocol was approved by Ethics Committee of Yantai Hospital (Yantai, Shandong Province, China). Informed consent was obtained from patients' parents. 40 children of both sex with the American Society Anesthesiologists physical status I-II, aged 4-12 years, weighing 80% to 120% of the standard weight, undergoing ventricular septal and atrial septal defect repair, were recruited. Exclusion criteria were unstable medical condition, such as severe pulmonary hypertension, cardiac right-to-left shunts, respiratory system and mental disorders. Children were randomly allocated into two groups: intravenous induction (Group C) and sevoflurane intubation group (Group D).

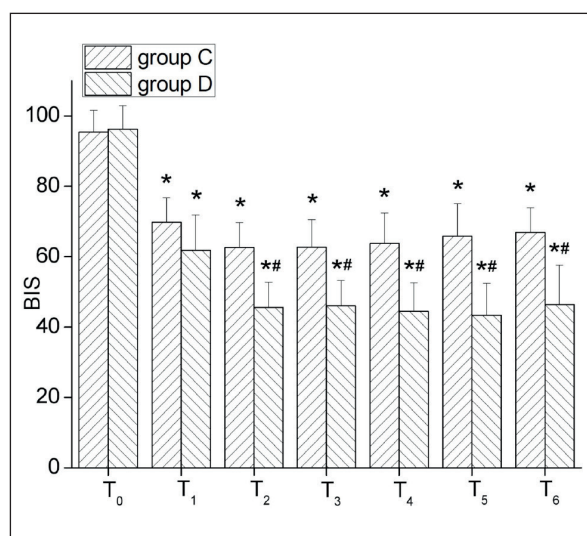
### Methods

All patients were administered with pre-operative fasting for 4-6 h, forbidden to drink for 2-3 h, without any pre-medication drugs. On admission

to the operating room, heart rate (HR), peripheral O<sub>2</sub> saturation (S<sub>p</sub>O<sub>2</sub>), non-invasive blood pressure (BP), electrocardiography (ECG), and bispectral index (BIS) were monitored. Patients in Group C received midazolam (Jiangsu Nhwa Pharmaceutical Corporation Co. Ltd, Xuzhou, China) 0.1 mg/kg, pipecuronium (Gedeon Richter Plc., Budapest, Hungary) 0.1 mg/kg, and fentanyl (Yichang Humanwell Pharmaceutical Co. Ltd, Yichang, China) 5-8 µg/kg. After the loss of consciousness, mechanical ventilation was implemented and radial artery catheterization was conducted. Mean arterial pressures (MAPs) were measured and recorded. Endotracheal intubation was performed in conventional manner by an attending physician with extensive clinical experience. Following the intubation, the respiration of patients was monitored with the anesthesia maintained with 1% × 2 L/min sevoflurane. Patients in Group D were administered inhalational anesthetics, 8% × 6 L/min sevoflurane via facemask. After the loss of consciousness, mechanical ventilation started, intravenous access was established, and radial artery catheterization was conducted. Endotracheal intubation was performed at 4 min after induction. MAPs were measured and recorded. After intubation, patients were intravenously administered with midazolam 0.1 mg/kg, pipecuronium 0.1 mg/kg, and fentanyl 5-8 µg/kg. 1% × 2 L/min sevoflurane was used to maintain anesthesia. The measurement times for the parameters of heart rate (HR) were T<sub>0</sub>, before induction; T<sub>1</sub>, loss of consciousness; T<sub>2</sub>, immediately before intubation; T<sub>3</sub>, intubation; T<sub>4</sub>, immediately after intubation; and T<sub>5</sub>, T<sub>6</sub> at 1 and 3 min after intubation. MAPs were measured at T<sub>2</sub>-T<sub>6</sub>. When loss of consciousness, 5 and 10 min after intubation, venous blood was collected for ET and Thromboxane A<sub>2</sub> (TXA<sub>2</sub>) analysis by Sn-695B radioimmunoassay counter (Shanghai Hesuo Rihuan Photoelectric Instrument Co., Ltd., Shanghai, China). TXA<sub>2</sub> with half-life of 30 s can be rapidly metabolized into inactive thromboxane B<sub>2</sub> (TXB<sub>2</sub>); therefore, the level of TXB<sub>2</sub> was considered as the index to assess TXA<sub>2</sub> concentration<sup>[10]</sup>.

### Statistical Analysis

Statistical analysis was implemented using SPSS18.0 for windows (SPSS Inc., Chicago, IL, USA). All data were reported as the mean ± SD, and differences between groups were evaluated by one-way analysis of variance (ANOVA) followed by Tukey's multiple range test. The level of statistical significance was set at  $p < 0.05$ .



**Figure 1.** BIS values at different time points. Data were presented as means ± SD \* $p < 0.05$  vs. T<sub>0</sub>; \*\* $p < 0.05$  vs. group C.

### Results

The data of 40 patients were evaluated in the study (Figure 1). No statistically significant difference was determined between the groups in respect of patient characteristics and ASA scores ( $p > 0.05$ ; Table I). In the follow-up visits after surgery, no children experienced vomiting and laryngospasm, and glottis exposure was excellent or good. In Group D, we found two children who showed signs of cough and limb movement disorder, also if endotracheal intubation was conducted successfully. HR and MAP were kept in the safe range at each time point. As illustrated in Figure 1A, the HR values in Group C at T<sub>2</sub>, T<sub>3</sub>, T<sub>4</sub> and T<sub>6</sub> were statistically significantly lower compared to the values at T<sub>0</sub> ( $p < 0.05$ ). MAP values at T<sub>5</sub> and T<sub>6</sub> were significantly increased compared to the values at T<sub>2</sub> ( $p < 0.05$ ) (Figure 2). In the comparison between groups, patients in Group D had a significant increase in HR values at T<sub>2</sub>, T<sub>3</sub> and T<sub>6</sub> ( $p < 0.05$ ) along with a greater fall in MAP values at T<sub>5</sub>. Both groups had a significant

reduction in BIS at T<sub>1</sub>-T<sub>6</sub> compared to the values at T<sub>0</sub> ( $p < 0.05$ ) (Figure 1B). Compared to Group C, patients in Group D had a significant reduction in BIS at T<sub>2</sub>-T<sub>6</sub> ( $p < 0.05$ ), while no differences were found at other time points ( $p > 0.05$ ). As illustrated in Table II, both groups had normal ET and TXB2 concentration at each time point. There were no significant differences between groups as well as intergroup comparison of different time points.

### Discussion

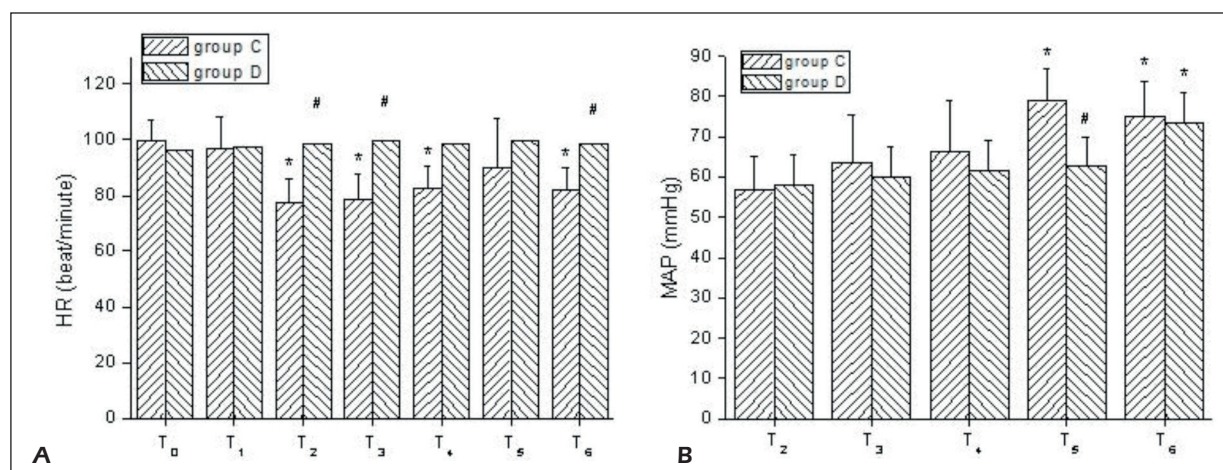
It is well known that intracardiac shunt could decrease the effect of inhalational anesthesia induction<sup>11</sup>; therefore, children with congenital left-to-right intra-cardiac shunt were investigated in this research. Investigations have shown that anesthesia induction by using sevoflurane in high-flow oxygen provided the satisfactory conditions for oral or nasal intubation conditions in infants with congenital heart disease<sup>12</sup>. Increasing literature confirmed that sevoflurane combined with intravenous anesthetics, such as remifentanyl, could inhibit the stress response to endotracheal intubation<sup>13</sup>. Based on Cagiran et al<sup>13</sup> and Wappler's et al<sup>14</sup> findings, endotracheal intubation surgery via anesthesia induction was carried out by using 8% × 6 L/min sevoflurane in oxygen, and the effects of only sevoflurane induction on inhibiting the stress response to endotracheal intubation were observed. Our data demonstrated that intubation was finished successfully with excellent or good glottis exposure. After surgery, no vomiting and laryngospasm were observed in children. Although in two children were found signs of cough and limb movement disorder in Group D, intubation was still completed successfully. Hemodynamic changes of HR and MAP are a reflection of stress sensitive indicators during intubation<sup>15,16</sup>. Since children displayed a low degree of adaptability in radial artery puncture under waking state, BP cuff was measured on admission to the operating room. After the loss of consciousness, radial artery catheterization was

**Table I.** Demographic data.

Groups	Age (years)	Height (cm)	Weight (kg)	Sex (male/female)	Type of surgery (ventricular septal/septal defect/repair)	ASA physical status (I/II)
Group C (n=20)	7.4±2.6	118.5±15.2	21.3±6.0	10/10	14/6	15/5
Group D (n=20)	7.6±2.7	123.2±13.0	21.9±4.6	10/10	15/5	16/4

Values are given as Mean ± SD.  $p < 0.05$  was considered statistically significant. There were no significant differences between the two groups.





**Figure 1.** BIS values at different time points. Data were presented as means  $\pm$  SD \* $p$ <0.05 vs. T<sub>0</sub>; # $p$ <0.05 vs. group C.

conducted and MAPs were measured. The changes of MAPs before and after intubation can indicate stimulus intensity of intubation, so only MAPs were selected for statistical comparison. Our data showed the indexes of HR in Group D have no markedly difference in contrast to the values at T<sub>0</sub>, and this may be explained in part with high concentrations of sevoflurane. Sevoflurane was proven to be effective in reducing peripheral vascular resistance in a dose-dependent manner, following reflection to peripheral expansion caused an increase in HR<sup>16</sup>. HR at T<sub>2</sub>, T<sub>3</sub>, T<sub>4</sub> and T<sub>6</sub> in Group C significantly decreased in comparison to the values at T<sub>0</sub>, while no significant reduction at T<sub>5</sub> was detected. Moreover, HR change range was higher in comparison to Group D. Before and after intubation, MAP in both of the groups significantly increased, in which the changes were more obvious in Group C, especially at T<sub>5</sub>. These results suggest that sevoflurane have an advantage in abolishing cardiovascular reactivity to endotracheal intubation. Although BIS may be significantly different in children at different ages, significant correlation was demonstrated between BIS and anesthesia sedation<sup>17,18</sup>. BIS monitoring has been recognized as an important predictor for

anesthesia sedation during anesthesia induction. In this work, we found that BIS values in Group C were 60-70, while they were 40-50 in Group D. BIS values in Group D were significantly decreased in contrast to Group C, suggesting that Group D exerted a better sedative effect before and after intubation. Slight changes in BIS values before and after intubation might be related to cerebral blood flow via changes in blood pressure under intubation stimulation<sup>19</sup>. ET and TXA2 are two independent indicators that were used to assess stress response<sup>3,10,20</sup>. Responses to stressors can lead to transcription of the endothelin-1 mRNA and ET, which are synthesized and secreted in a few minutes<sup>21</sup>. ET and TXB2 concentration, at loss of consciousness, 5 min and 10 min after intubation, were measured. Our data showed no significant difference in ET and TXB2 concentration before and after intubation. These results may be associated with high concentrations of sevoflurane in Group D and plenty of fentanyl, which suppressed the stress in response to endotracheal intubation<sup>22</sup>. Further, these results illustrate that inhalational sevoflurane anesthesia induction effectively suppressed the stress response to endotracheal intubation.

**Table II.** ET and TXB2 concentration at different time points.

Groups	ET (pg/ml)			TXB <sub>2</sub> (pg/ml)		
	Loss of consciousness	5 min after intubation	10 min after intubation	Loss of consciousness	5 min after intubation	10 min after intubation
Group C (n=20)	42.1 $\pm$ 10.0	41.2 $\pm$ 11.1	43.6 $\pm$ 14.2	69.3 $\pm$ 27.9	55.1 $\pm$ 24.0	73.5 $\pm$ 32.8
Group D (n=20)	42.7 $\pm$ 12.0	44.8 $\pm$ 10.7	42.1 $\pm$ 10.7	56.1 $\pm$ 17.2	60.5 $\pm$ 34.1	60.7 $\pm$ 21.8

Values are given as Mean  $\pm$  SD.  $p$ <0.05 was considered statistically significant. There were no significant differences between the two groups.

## Conclusions

Compared to intravenous anesthesia induction, endotracheal intubation received by children with congenital heart disease via inhalational sevoflurane anesthesia induction could maintain more stable hemodynamics, including HR and MAP values, improving the quality of anesthesia. Sevoflurane anesthesia induction attenuates the stress response to endotracheal intubation in children with congenital heart disease.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

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