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Effects of different doses of alfentanil on cardiovascular response to rapid sequence intubation in elderly patients: a parallel-controlled randomized trial

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Abstract

Background Rapid sequence intubation (RSI) have been shown to be effective in preventing reflux aspiration in patients with a full stomach during anaesthesia induction and endotracheal intubation. However, there is currently no standardized operation protocol or anaesthesia induction drug standard for RSI. Furthermore, there is a lack of evidence regarding the use of RSI in patients older than 65. In this study, we aimed to investigate the cardiovascular effects of different doses of alfentanil combined with propofol and etomidate during RSI in elderly patients aged 65–80 years.

Methods A total of 96 patients aged 65–80 years who underwent general anaesthesia with tracheal intubation were selected for this study. The patients were randomly assigned to one of four groups using a random number table. Group A patients received an induction dose of 10 μg/kg alfentanil, group B patients received 15 μg/kg alfentanil, group C patients received 20 μg/kg alfentanil, and group D patients received 25 μg/kg alfentanil. Heart rate (HR), mean arterial pressure (MAP), cardiac index (CI), and ejection fraction (EF) were measured at three time points: 5 min before anaesthesia induction (T0), 1 min after endotracheal intubation (T1), and 5 min after endotracheal intubation (T2). Concurrently, 4 ml of arterial blood was collected from patients at three time points, and the concentrations of norepinephrine (NE) and cortisol (Cor) in plasma were detected. Occurrences of hypertension, hypotension, bradycardia and tachycardia during anesthesia induction to 5 min after tracheal intubation were noted.

Results Compared with T0, the HR, MAP, NE and Cor concentrations in group A and group B were increased at the T1 and T2 time points, CI and EF values were decreased ($P < 0.05$). HR and MAP in groups C and D were increased at the T1 time point, while they were decreased at the T2 time point in group D ($P < 0.05$). The changes in CI and EF values, concentrations of NE and Cor, were not significant at T1 and T2 time points in group C ($P > 0.05$). Additionally, they were not significant in group D at the T1 time point ($P > 0.05$), but decreased at the T2 time point ($P < 0.05$). Compared with group A, the HR, MAP, NE and Cor concentrations in groups C and D were decreased at T1 and T2 time points

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($P < 0.05$). The CI and EF values of groups C and D were increased at T1 time point but decreased at T2 time point in group D ($P < 0.05$). The incidence of hypertension and tachycardia in group A was significantly higher than that in group C and group D ($P < 0.05$), and the incidence of hypotension and bradycardia in group D was significantly higher than that in group A and group B ($P < 0.05$).

Conclusion Alfentanil 20 μg/kg for RSI in elderly patients, can effectively inhibit the violent cardiovascular reaction caused by intubation, and avoid the inhibition of cardiovascular system caused by large dose, hemodynamics more stable.

Trial registration ChiCTR2200062034 (www.chictr.org.cn).

Keywords Alfentanil, Rapid sequence intubation, Etomidate, Propofol, Haemodynamic, Elderly patients

Background

RSI is defined as the use of intravenous anaesthetics and muscle relaxant drugs with a rapid onset to make the patient's consciousness and spontaneous breathing disappear in a short period, producing muscle relaxation and satisfactory conditions for tracheal intubation [1]. The purpose is to provide good conditions for tracheal intubation for patients at high risk of full stomach and aspiration, especially in emergency situations, to prevent the occurrence of aspiration. RSI plays an important role in ensuring airway safety for critically ill patients. However, the release of catecholamines in vivo due to laryngoscope exposure and tracheal intubation often causes dramatic hemodynamic fluctuations [2]. Patients mainly exhibit the release of much catecholamines, increased blood pressure, and accelerated HR [2, 3]. For normal middle-aged and young people, short-term haemodynamic fluctuations may be insignificant, but for elderly patients, especially those with underlying cardiovascular and cerebrovascular diseases, the severe haemodynamic fluctuations caused by tracheal intubation may have irreversible and serious consequences [4, 5]. Studies have shown that perioperative hypotension and hypertension both increase the occurrence of adverse events in patients after surgery, and even short-term hypotension may increase the occurrence of adverse reactions after surgery [6, 7]. For elderly patients, it is worth discussing what dose of medication may be used to achieve RSI while maintaining haemodynamic stability and preventing complications.

The drugs used in RSI mainly include rapidly effective intravenous induction agents, muscle relaxants, and opioid analgesics [8]. Opioids play an important role in inhibiting the stress response of tracheal intubation and reducing the severe haemodynamic fluctuations caused by catecholamine release during tracheal intubation [9, 10]. Studies have shown that 65.9% of adult patients and 54.9% of paediatric patients use opioid drugs during RSI [11]. Alfentanil is a synthetic opioid with strong analgesic effects, fast onset, and short duration of action. Its onset time is 3–4 times faster than fentanyl and sufentanil, with a peak effect occurring 1.4 min after intravenous administration and a duration of 10–15 min. It is suitable for RSI. Studies on alfentanil for RSI have shown that the optimal dose range of alfentanil is 33.4–39.4 μg/kg in adult patients under 65 years old [12]. Alfentanil was introduced to China relatively late and has been mainly used for short surgeries, with no reported use for RSI in elderly patients. In this study, we not only compare the effects of different doses of alfentanil on blood pressure, HR, and catecholamine release but also monitor real-time CI and cardiac EF using ultrasound to evaluate the impact of different doses of alfentanil on cardiac function during RSI in elderly patients. We aim to explore the feasibility of using different doses of alfentanil for RSI in elderly patients as well as its impact on cardiovascular responses, providing a reference for clinical practice.

Methods and materials

Ethics and registration

Ethical approval for this study (ethics: PJ-KY2022-11) was provided by the Ethics Committee of the First People's Hospital of Yichang, China, on 31 May 2022. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2200062034) on 20/07/2022 before enrolment. The study protocol followed the CONSORT guidelines. All participants signed written informed consent.

Patient inclusion and exclusion criteria

We included patients aged between 65 and 80 years with an American Society of Anesthesiologists (ASA) physical status of I or II and a body mass index (BMI) range from 18 kg/m^2 to 24 kg/m^2 who were undergoing elective surgery under general anaesthesia, clearly understood and voluntarily participated in the study, and signed the informed consent form. Patients were excluded for the following reasons: hypertension, cardiovascular and cerebrovascular disease, previous history of difficulty intubating or difficult airway, gastroesophageal reflux disease or full stomach, endocrine disease, severe hepatic or renal dysfunction, neuromuscular disease, analgesic drug dependence or history of drug use.

Grouping and processing

The patients included in the study were randomly assigned to one of four experimental groups (Group A, Group B, Group C and Group D) in a 1:1:1:1 ratio by a computer-generated random allocation sequence, and a specific researcher enrolled participants by random number in an opaque envelope. The groups were: group A (10 μg/kg alfentanil), group B (15 μg/kg alfentanil), group C (20 μg/kg alfentanil), and group D (25 μg/kg alfentanil). Noninvasive arterial blood pressure, blood oxygen saturation (SpO2) and electrocardiogram were routinely monitored after admission, midazolam was given at 2 mg intravenously, and invasive artery blood pressure was continuously monitored by radial artery puncture and catheterization under local anaesthesia. The left ventricular end-systolic diameter, left ventricular end-diastolic diameter, maximum diameter of the left ventricular outflow tract and HR were measured at the parasternal left ventricular long axis section, and the time integral of aortic flow velocity was measured at the five-chamber incision plane of the apex of the heart by a doctor with independent ultrasonic diagnostic qualifications at 5 min before anaesthesia induction (T0), 1 min after endotracheal intubation (T1), and 5 min after endotracheal intubation (T2). We measured the above data with SonoSite M-turbo sonographer and calculated the CI and EF with its own program. An anaesthesia nurse recorded the patient's MAP and HR and collected 4 ml of arterial blood from each patient at each time point. An anaesthesiology nurse formulated different concentrations of afentanil for the subjects according to random number table grouping. To maintain the consistent appearance of injected drugs, the same drug volume of alfentanil was delivered by injection in each group while varying the formulation as follows: group A (100 μg/ml), group B (150 μg/ml), group C (200 μg/ml), and group D (250 μg/ml). Information was not shared between the anaesthesiologist who administered the drug, the two anaesthesiology nurses and the sonographer.

Anaesthesia method

After the patients completed the first data collection, oxygen was administered to the patient's mask under the condition of spontaneous breathing, with an oxygen flow rate of 5 L/min and the oxygen concentration was 100%. Five minutes later, an Etomidate-Propofol mixture (Etomidate 1 mg/ml and propofol 5 mg/ml) 0.2 ml/kg was injected intravenously, and the injection was completed within 5 s. Alfentanil injection (0.1 ml/kg) was completed within 20 s; rocuronium (0.6 mg/kg) was injected within 5 s. After the patient lost consciousness and muscle relaxation, the endotracheal tube was inserted through the mouth and secured with the assistance of a video laryngoscope. The anesthesia machine was then connected for mechanical ventilation. The mechanical ventilation was performed using a volume-controlled ventilation mode, with adjustments made to the ventilation parameters in order to maintain a tidal volume of 6–8 ml/kg, respiratory rate 8–12 times/min, inspiratory/expiratory 1:2, end-tidal CO_2 partial pressure 35–45 mmHg, and SpO_2 greater than 95%. No surgery was performed within 5 min after intubation. Additionally, no additional fluids were given beyond the fluid infusion needed to meet the induction of anesthesia, and no additional medications other than those used for the induction of anesthesia were administered. Five minutes after tracheal intubation, if MAP < 65 mmHg or systolic blood pressure < 90 mmHg during the process, hypotension was recorded, and 40 μg of norepinephrine was given intravenously after data collection. If blood pressure increased by more than 30% of the baseline value, or if SBP was ≥ 140 mmHg or DBP was ≥ 90 mmHg, it was recorded as hypertension, and appropriate anesthesia was increased after data collection. If HR < 60 times/min, bradycardia was recorded, and 0.3 mg of atropine was given intravenously after data collection. If HR was > 100 times/min or greater than 20% of the baseline value, tachycardia was recorded, and appropriate anaesthesia was increased or 10 mg of esmolol was given intravenously after data collection. Patient sex, age, BMI, and ASA classification were recorded. The incidents of hypertension, hypotension, bradycardia and tachycardia was recorded during anesthesia induction to 5 min after tracheal intubation.

EF and CI value measurement

A phased array probe with a frequency of 1.5-4.0 MHz was used. The probe was placed in the long axis section of the 3/4 rib beside the sternum, and the M-sample line was positioned between the mitral valve tip and the tendinous cord and perpendicular to the major axis of the left ventricle. Left ventricular end diastolic meridian (Dd) and end systolic meridian (Ds) were measured, and left ventricular volume was calculated using the Teichholtz correction formula ($V=(7.0/2.4+D)\times D^3$). The EF value calculation formula is EF (%) = (Vd-Vs)/Vd ×100%. Deflecting the probe to clearly show the aortic root, we froze the image when the aortic valve was opened to its maximum during the left ventricular systolic period, and the distance between the anterior and posterior walls of the aortic valve root was measured to obtain the maximum diameter of the left ventricular outflow tract (D). The probe was slid along the long axis of the heart and rotated 90° clockwise at the apex of the heart to obtain the apex four-chamber cardiac plane. By pressing the probe tail up and down on the four-chamber core base, the five-chamber core section of the apex of the heart was obtained, and the left ventricular outflow tract was displayed. In pulsed Doppler mode, the sampling volume

was placed in the left ventricular outflow tract below the aortic valve, and the window width was set at 2–4 mm. Pulsed Doppler mode (PW) was selected to trace the aorta blood flow velocity time integral image. The velocity time integral (VTI) of the aorta blood flow velocity was calculated by using an ultrasonic program. The average stroke volume (SV) was calculated by taking 3 to 5 consecutive images during the same breathing cycle. The stroke volume (SV) was calculated as SV=VTI×πD. Heart rate and body surface area (BSA=1.05+ (body weight −30) ×0.02) were used to calculate cardiac displacement and cardiac index. The cardiac output (CO) was calculated as CO=SV×HR. The cardiac index (CI) was calculated as CI=CO/BSA.

Blood sample processing

Arterial blood (4 ml) was collected with an EDTA anticoagulant tube at three time points: T0, T1, and T2, and the blood samples were centrifuged for 15 min within 30 min after collection. The plasma samples were stored at -80℃. Enzyme-linked immunosorbent assay (ELISA) was used to detect the concentrations of NE and Cor in the plasma samples.

Sample size estimate

We used PASS Sample Software(Version 15; NCSS, LLC, Kaysville, Utah, USA) to estimate the sample size. According to the preliminary experiment, the increase of MAP in group A, group B, group C and group D at t_1 were 18.5±10.8, 11.3±7.8, 8.5±5.5, and 6.2±5.3, respectively. Our calculations indicated that 21 patients in each group would be required, the test level was set at 0.05 (two-sided) and the test power was 0.90. Because ultrasonic measurement data collection is difficult, we set a 20% shedding rate and determined that 100 samples should be included.

Statistical analysis

Statistical analysis was performed using SPSS Software(Version 21.0; IBM Corporation, New York). Normally distributed measurement data were expressed as the mean±standard deviation. One-way ANOVA was used for the comparison of the four groups. Repeated-measures ANOVA was used for the repeated-measures data, and the LSD test was used for pairwise comparisons within and between groups. For the qualitative data, the Chi-square test and Fisher's exact probability method were used for comparisons between groups. Differences were considered statistically significant at $P<0.05$. Statistical charts were drawn by GraphPad Prism Software (Version 5.01, GraphPad Software, Boston, MA 02110, USA).

Results

One patient from each group was excluded from the study due to incomplete data collection. Therefore, data from a total of 96 patients were analyzed (Fig. 1). There were no statistically significant differences in sex, age, BMI or ASA grade between the four groups (Table 1).

Different groups and time points comparisons of HR and MAP

The HR and MAP at three time points were compared among the four groups of patients. As shown in Fig. 2, there were significant differences in HR and MAP at different time points (F=200.199, $P<0.001$; F=63.290, $P<0.001$) and differences between the four groups (F=14.604, $P<0.001$; F=8.392, $P<0.001$) after repeated-measures ANOVA. Furthermore, the trends of HR and MAP were also different among the four groups (F=41.824, $P<0.001$; F=19.759, $P<0.001$). LSD pairwise comparison found that: compared with T0 time point, the HR and MAP of the four groups were increased at the T1 time point ($P<0.05$;), and they were still higher at the T2 time point in group A and group B ($P<0.05$) but decreased in group D ($P<0.05$) (Table 2). Compared with T0 time point there was no significant difference in HR and MAP at T2 in group C ($P>0.05$). Compared with group A, HR and MAP were significantly decreased at the T1 and T2 time points in groups C and D ($P<0.05$) (Table 2).

Different group and time-point comparisons of CI and EF values

The CI and EF at three time points were compared among the four groups of patients. As shown in Fig. 3, there were significant differences in the CI and EF values at different time points (F=50.338, $P<0.001$; F=18.513, $P<0.001$) after repeated-measures ANOVA. And the trends of CI and EF were also different among the four groups (F=27.627, $P<0.001$; F=20.631, $P<0.001$). LSD pairwise comparison found that: compared with T0, CI and EF values were decreased in group A and group B at the T1 and T2 time points ($P<0.05$). The changes in group C and group D were not significant at the T1 time point ($P>0.05$), but they decreased in group D at the T2 time point ($P<0.05$) (Table 2). Compared with group A, CI and EF values were significantly increased at T1 time point in group C and D ($P<0.05$), but decreased atT2 time point in group D ($P<0.05$) (Table 2).

Different group and time-point comparisons of NE and Cor concentrations

The NE and Cor concentrations at three time points were compared among the four groups of patients. As shown in Fig. 4, there were significant differences in NE and Cor concentrations at different time points (F=43.922,

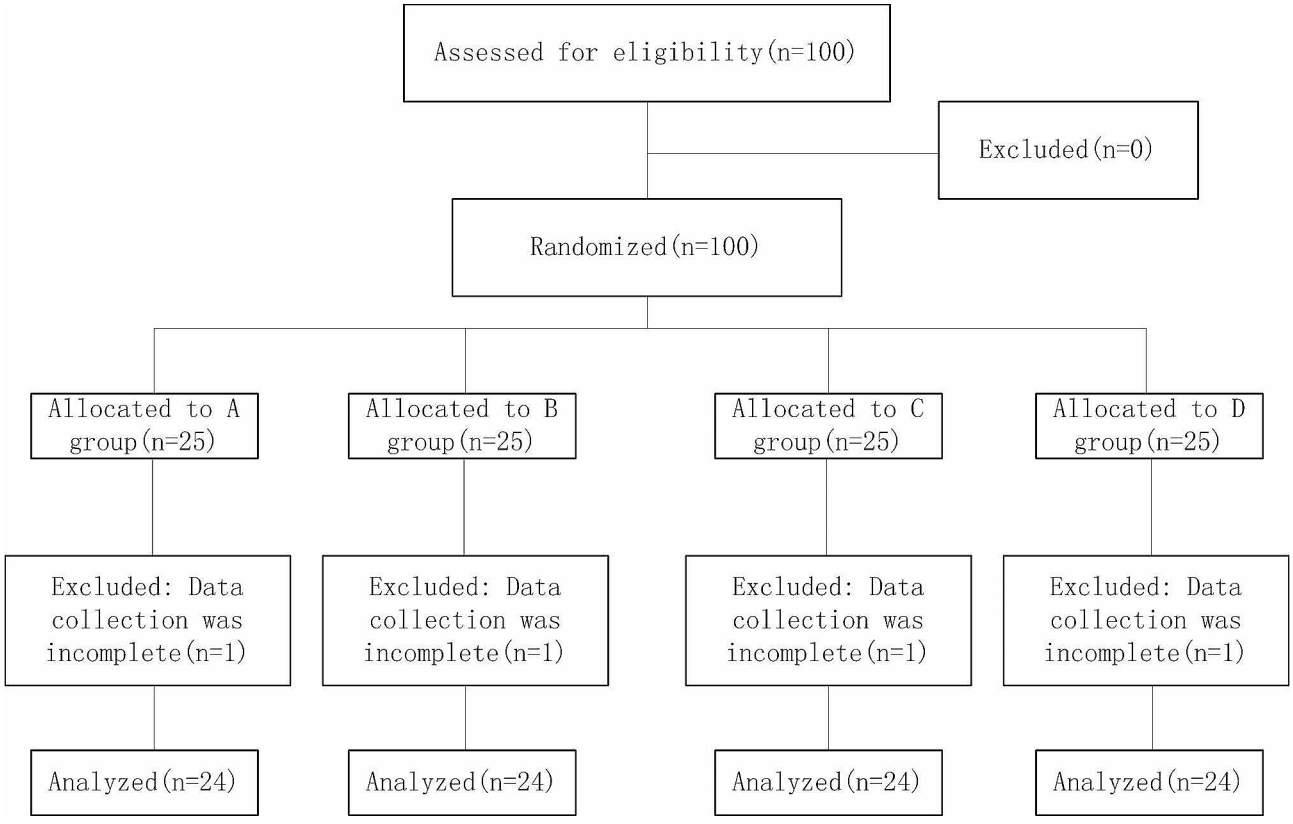

Fig. 1 Flow diagram of patients through the trial

Table 1 Baseline patient characteristics

Grouping	Group A (*n* = 24)	Group B (*n* = 24)	Group C (*n* = 24)	Group D (*n* = 24)	*P* Value
Age (y)	69.5 ± 3.8	69.8 ± 3.7	70.1 ± 4.0	69.7 ± 4.6	0.938
BMI (kg/m^2)	21.6 ± 1.6	21.9 ± 2.0	21.7 ± 1.8	21.8 ± 1.7	0.931
ASA					0.904
I	8 (33.3)	6 (25.0)	7 (29.2)	6 (25.0)	
II	16 (66.7)	18 (75.0)	17 (70.8)	18 (75.0)	

BMI, body mass index; ASA, American Society of Anesthesiologists. Data are summarised by number (%) or mean (standard deviation). $P<0.05$ was considered statistically different

$P<0.001$; F=28.001, $P<0.001$) after repeated-measures ANOVA. And the trends of NE and Cor concentrations were also different among the four groups (F=17.263, $P<0.001$; F=11.534, $P<0.001$). LSD pairwise comparison found that: compared with T0, NE and Cor concentrations were increased in group A and group B at the T1 and T2 time points ($P<0.05$). The changes in group C and group D were not significant at the T1 time point ($P>0.05$), but they decreased in group D at the T2 time point ($P<0.05$) (Table 2). Compared with group A, NE and Cor concentrations were significantly decreased at T1 and T2 time points in groups C and D ($P<0.05$) (Table 2).

Group comparison of adverse reactions

The adverse reactions of patients intraoperatively, such as intraoperative hypertension, bradycardia and tachycardia, were recorded and compared among the four groups. As shown in Table 3, Fisher's exact probability analysis showed significant differences in the incidence of perioperative hypotension, hypertension, bradycardia and tachycardia between the four groups ($P<0.05$). Compared with groups A and B, the incidence of hypotension and bradycardia in group D was higher ($P<0.05$). Compared with groups C and D, the incidence of hypertension in group A was higher ($P<0.05$). Compared with group D, the incidence of tachycardia in group A was higher ($P<0.05$).

Discussion

Intravenous anaesthetics and opioids used for RSI have inhibitory effects on cardiovascular function and the autonomic nervous system in elderly patients. While RSI is applied to achieve good intubation conditions, its fundamental goal is to maintain stable circulatory function by appropriately suppressing the high reactivity of the autonomic nervous system during intubation using suitable drugs and doses. In this study, we selected a combination of propofol-etomidate mixture, rocuronium bromide, and different doses of alfentanil that not only

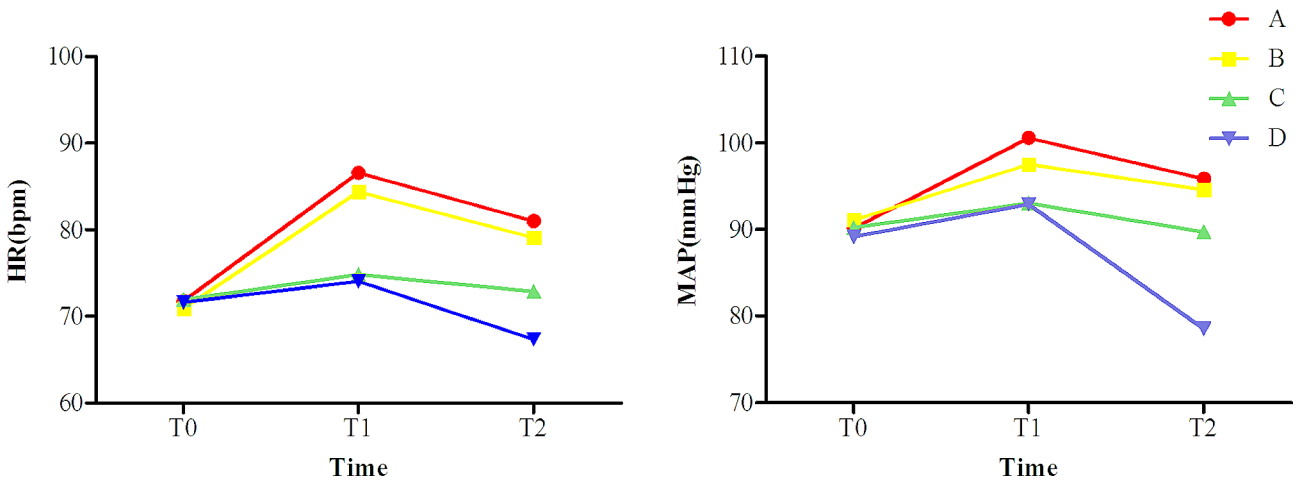

Fig. 2 Changes in the HR and MAP over time in four groups ($P<0.001$). T0: 5 min before anaesthesia induction, T1: 1 min after endotracheal intubation, T2: 5 min after endotracheal intubation

Table 2 Different group and time-point comparisons of HR, MAP, CI, EF values, NE and Cor concentrations

Grouping	Group A ($n=24$)	Group B ($n=24$)	Group C ($n=24$)	Group D ($n=24$)	*P* Value
HR(bpm)					
T0	71.8 ± 5.5	70.9 ± 4.6	72.0 ± 6.5	71.6 ± 5.4	0.917
T1	86.6 ± 7.5[a]	84.4 ± 4.2[a]	74.8 ± 6.1[ab]	74.0 ± 5.7[ab]	0.000
T2	81.0 ± 6.5[a]	79.1 ± 5.2[a]	72.9 ± 6.0[b]	67.3 ± 6.0[ab]	0.000
MAP(mmHg)					
T0	90.2 ± 8.0	91.1 ± 6.5	90.2 ± 8.8	89.2 ± 5.8	0.846
T1	100.6 ± 7.6[a]	97.5 ± 5.9[a]	93.0 ± 8.2[ab]	92.9 ± 5.8[ab]	0.000
T2	95.8 ± 9.8[a]	94.6 ± 6.0[a]	89.7 ± 8.1[b]	78.5 ± 7.9[ab]	0.000
CI(L/min · m^2)					
T0	3.3 ± 0.3	3.4 ± 0.4	3.3 ± 0.2	3.2 ± 0.4	0.248
T1	3.0 ± 0.3[a]	3.1 ± 0.3[a]	3.4 ± 0.2[b]	3.3 ± 0.4[b]	0.000
T2	3.2 ± 0.2[a]	3.2 ± 0.3[a]	3.3 ± 0.3	2.9 ± 0.3[ab]	0.000
EF(%)					
T0	60.4 ± 4.1	62.0 ± 4.6	61.4 ± 4.5	59.7 ± 4.5	0.315
T1	56.2 ± 4.2[a]	58.4 ± 5.7[a]	62.4 ± 4.8[b]	60.8 ± 4.8[b]	0.000
T2	59.1 ± 3.8[a]	59.5 ± 4.8[a]	62.0 ± 3.7	55.5 ± 4.4[ab]	0.000
NE(ng/ml)					
T0	171.6 ± 52.0	178.4 ± 68.3	171.4 ± 53.1	170.2 ± 57.4	0.961
T1	211.7 ± 43.4[a]	200.7 ± 62.8[a]	174.7 ± 49.5[b]	173.4 ± 56.3[b]	0.031
T2	204.7 ± 43.1[a]	192.8 ± 65.7[a]	169.3 ± 48.8[b]	159.8 ± 55.7[ab]	0.018
Cor(pg/ml)					
T0	83.6 ± 24.2	84.0 ± 25.7	83.1 ± 24.9	83.5 ± 24.5	0.985
T1	99.1 ± 21.0[a]	95.8 ± 25.9[a]	85.3 ± 20.6[b]	82.3 ± 25.0[b]	0.029
T2	94.8 ± 21.7[a]	90.1 ± 24.5[a]	81.0 ± 20.5[b]	77.2 ± 21.4[ab]	0.026

T0: 5 min before anaesthesia induction, T1: 1 min after endotracheal intubation, T2: 5 min after endotracheal intubation. Data are summarised by mean (standard deviation)

[a] Compared with T0, $P<0.05$. [b] Compared with Group A, $P<0.05$

met the requirements of RSI but also provided a more stable haemodynamic maintenance scheme. Wang C. [13] found that etomidate emulsion is physically and chemically compatible with propofol emulsions for up to 24 h at 4 °C, 25 °C, and 37 °C. And they suggested that etomidate and propofol can be administered in a mixture without adversely affecting each other. Currently, studies have shown that the use of a propofol-etomidate mixture for induction can reduce the hypotension and injection pain caused by propofol alone as well as reduce adverse reactions such as muscle spasms and postoperative nausea and vomiting caused by etomidate alone [14, 15].

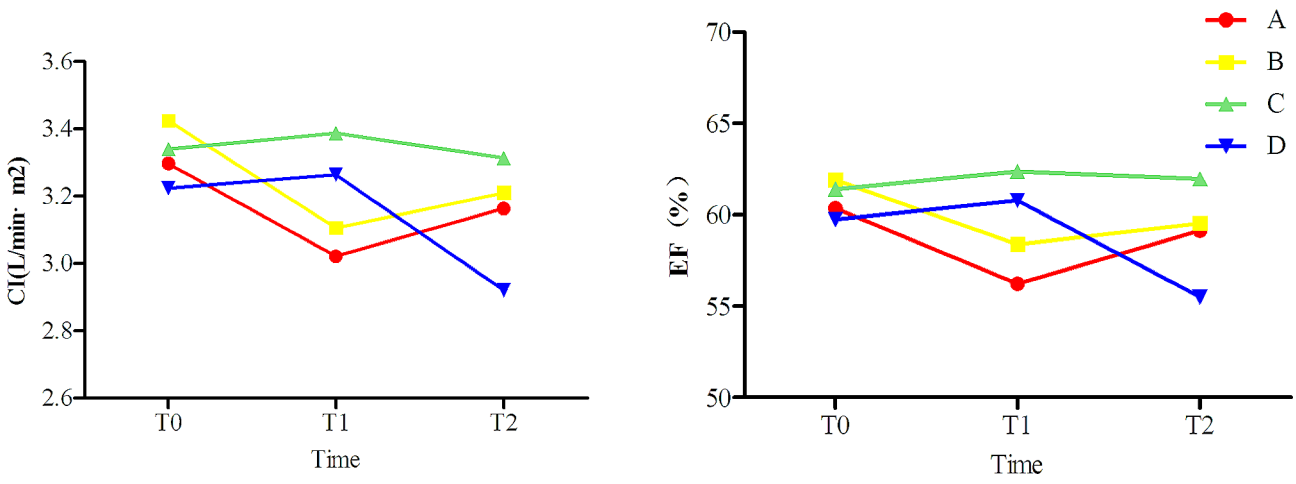

Fig. 3 Changes in the CI and EF value over time in four groups ($P < 0.001$). T0: 5 min before anaesthesia induction, T1: 1 min after endotracheal intubation, T2: 5 min after endotracheal intubation

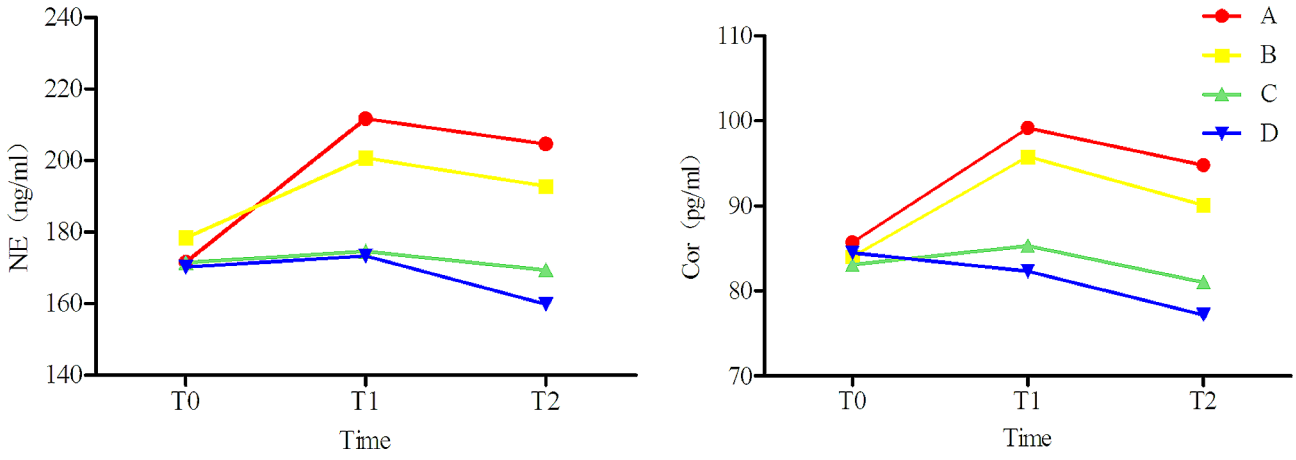

Fig. 4 Changes in the NE and Cor concentrations over time in four groups ($P < 0.001$). T0: 5 min before anaesthesia induction, T1: 1 min after endotracheal intubation, T2: 5 min after endotracheal intubation

Table 3 Cases of adverse reactions in the four groups

Grouping	Group A (*n* = 24)	Group B (*n* = 24)	Group C (*n* = 24)	Group D (*n* = 24)	χ^2 value	*P* Value
Hypotension	1(4.2)	1(4.2)	4(16.7)	8 (33.3)	9.744	0.015
Hypertension	9 (37.5)	5 (20.8)	2(8.3)	1 (4.2)	10.204	0.016
Bradycardia	1 (4.2)	2 (8.3)	5 (20.8)	8 (33.3)	8.401	0.041
Tachycardia	8(33.3)	6(25.0)	3(12.5)	1 (4.2)	7.890	0.045

Data are summarised by number (%)

The study by Liu Y. [16] also showed that the use of a 1:1 ratio of propofol and etomidate mixture for anesthesia induction and maintenance during endoscopy in elderly hypertensive patients resulted in a more stable cardiopulmonary function and fewer side effects during the perioperative period.

The release of catecholamines caused by laryngoscopy exposure and tracheal intubation is the fundamental cause of severe haemodynamic fluctuations during the intubation process, mainly manifested as increased blood pressure and HR [2, 17]. This reaction was most obvious when the catecholamine concentration reached its peak 1 min after intubation, and when the catecholamine concentration decreased 5 min after intubation, the patient's blood pressure and HR gradually decreased. [10, 18]. Therefore, we chose to collect blood samples from patients at 1 min and 5 min after intubation for testing. Currently, opioid drugs are still the main medications used to suppress the stress response of tracheal intubation. For slow induction before adult tracheal

intubation, fentanyl and sufentanil are mainly used [19–21], while alfentanil and remifentanil are mainly used for RSI [5, 9, 22]. After intravenous injection of sufentanil and fentanyl, the time to reach peak drug concentration is approximately 3 min, and the time to reach plasma and effect-site equilibrium concentration is approximately 6 min [23]. When rapidly and intravenously infused at high doses, they can cause side effects such as coughing, chest wall rigidity, bradycardia, and hypotension [24, 25]. On the other hand, when alfentanil and remifentanil are intravenously injected, the time required to reach plasma and effect-site equilibrium concentration is approximately 1 min [23], making them more suitable for RSI. Studies by Habib AS [26] and Maguire AM [27] have found that compared to remifentanil, alfentanil was associated with a lower incidence of hypotension and bradycardia in elderly and hypertensive patients undergoing tracheal intubation, making it a better choice for RSI in elderly patients.

In this study, we observed that as the dose of alfentanil increased, the blood pressure, HR, NE and Cor concentrations decreased at 1 min after intubation. However, there were different changes in the CI and EF values. Compared to the 10 μg group and 15 μg group, the 20 μg/kg and 25 μg/kg groups had higher CI and EF values at 1 min after intubation. These changes exhibited significant differences but were within the physiological range and had some clinical reference value. We believe that this may be due to alfentanil inhibiting the excessive release of catecholamines in plasma during laryngoscopy exposure and tracheal intubation, reducing peripheral vascular resistance and cardiac afterload. Meanwhile, mild release of catecholamine in plasma exerts positive muscle strength and positive frequency effects on cardiomyocytes, and patients show a slight increase in HR, CI, and EF values. This is consistent with the conclusion obtained by Abou-Arab [10] and Miller et al.[28] in the RSI using thiopental sodium combined with alfentanil.

In this study, we observed that patients in the 20 μg/kg and 25 μg/kg groups had the smallest changes in MAP, HR, NE, and Cor at 1 min after tracheal intubation, indicating that the dose of alfentanil combined with propofol and etomidate at 20 μg/kg and 25 μg/kg was more reasonable for suppressing the stress response of RSI. However, we also observed that patients in the 25 μg/kg group showed significant decreases in MAP, HR, CI, and EF values at 5 min after tracheal intubation. These changes were not significant at 1 min after intubation but were more obvious at 5 min after intubation. This may be related to the inhibitory effects of excessive doses of alfentanil on the sympathetic nervous system and myocardium. In this study, a mixture of propofol and etomidate was used as a combination drug for elderly patients aged 65–80 years, while Miller and Abou-Arab used sodium thiopental as a combination drug for people aged 18–55 years. The weakened self-regulatory ability of the autonomic nervous system in elderly patients and changes in drug absorption, metabolism, and excretion make elderly patients more sensitive to opioid drugs, and the dosage needs to be reduced compared to middle-aged and young adults [29]. Due to the increased sensitivity of the cardiovascular and nervous systems of elderly patients to drugs, the incidence of perioperative hypotension, bradycardia, and decreased CI and EF values is higher when using high-dose opioid drugs (Table 3; Fig. 3). Therefore, based on the results of this study, we believe that alfentanil at a dose of 25 μg/kg can inhibit the stress response of tracheal intubation when combined with propofol and etomidate for RSI. However, it carries a risk of hypotension, bradycardia, and decreased CI and EF values. However, the administration of 20ug/kg of alfentanil during RSI has been found to effectively suppress the stress response associated with tracheal intubation, while maintaining normal values for ejection fraction and cardiac index. Additionally, this intervention promotes greater stability in perioperative blood pressure and heart rate.

Limitation

There are some limitations to this study. Firstly, considering the population in this study was over 65 years old, the dose of rocuronium bromide in the study protocol was 0.6 mg/kg, which was lower than 1-1.2 mg/kg in previous literature reports. Secondly, the main objective of this study is to apply RSI technology to elderly patients with a high risk of full gastric reflux and aspiration in the emergency department. However, this study did not include patients with a full stomach in the emergency department. Thirdly, elderly patients with cardiovascular diseases were excluded from this study. It is important to note that most patients who require RSI in clinical practice have cardiovascular diseases. For such patients, further study is needed to determine the dose of alfentanil required for RSI.

Conclusions

Various doses of alfentanil were used to induce different hemodynamic changes in RSI in elderly patients. Alfentanil 20 μg/kg combined with propofol and etomidate for RSI in elderly patients aged 65 and older, resulting in more stable perioperative hemodynamic changes.

Abbreviations

RSI	Rapid sequence intubation
HR	Heart rate
MAP	Mean arterial pressure
CI	Cardiac index
EF	Ejection fraction
T	Time point
NE	Norepinephrine

Cor	Cortisol
ASA	American Society of Anesthesiologists
BMI	Body mass index
SpO2	Blood oxygen saturation
Dd	Diastolic meridian
Ds	Systolic meridian
PW	Pulsed Doppler mode
VTI	Velocity time integral
SV	Stroke volume (SV)
BSA	Body surface area
CO	Cardiac output
ELISA	Enzyme-linked immunosorbent assay

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Author contributions
XB.C. and M.H. drafted the manuscript, performed the statistical analysis and designed the trial. AH.S., M.Z. and K.W. performed the study and obtained data. CX.C. contributed to data interpretation and analysis and were involved in revising the manuscript. All authors contributed substantially to its revision. All the authors have read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed according to the principles of the Helsinki Declaration on human experimentation. This study was approved by the Ethics Committee of the First People's Hospital of Yichang. Informed written patient consent was obtained from every participant in the current study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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