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ORIGINAL ARTICLE

Optimal fentanyl dosage for attenuating systemic hemodynamic changes, hormone release and cardiac output changes during the induction of anesthesia in patients with and without hypertension: a prospective, randomized, double-blinded study

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Abstract
Purpose The purpose of this study was to compare the dose-related effects of fentanyl on systemic hemodynamics, hormone release and cardiac output in response to endotracheal intubation in patients with and without hypertension.
Methods Forty-five patients without hypertension and 45 patients with hypertension (total 90 patients) undergoing elective general surgical, urological or gynecological procedures under general anesthesia were studied. The patients were randomly divided into three groups to receive either saline (control), 2.0 μg/kg fentanyl or 4.0 μg/kg fentanyl before tracheal intubation. Anesthesia was induced via intravenous target controlled infusion of propofol (plasma concentration, 4.0 μg/mL) followed by administration of the three drugs. Heart rate, blood pressure, and cardiac output were continuously monitored using Flo Trac/Vigileo system™ and Bispectral index from before anesthetic induction until 10 min after tracheal intubation.
Results In patients without hypertension, there was a significant difference in mean arterial pressure (MAP) among the three groups 2 min after intubation. Cardiac index (CI) in all three groups decreased before intubation compared with that in the awake period, returning to awake values after intubation in all three groups. There was a significant difference in CI between the 4 μg/kg fentanyl group and the other two groups immediately and 1 min after intubation.
In patients with hypertension, a differential time course of MAP changes was observed among the three groups after intubation. CI in the three groups decreased after the induction of anesthesia and increased after intubation in control and 2 μg/kg fentanyl groups compared with that in the awake period.
Conclusions The present study shows that it is preferable to administer 2 μg/kg fentanyl in patients without hypertension and 4 μg/kg fentanyl in patients with hypertension in order to minimize the changes in heart rate, systolic blood pressure and cardiac output associated with tracheal intubation.

Keywords Fentanyl dose · Cardiac output · Intubation · Hypertension

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Introduction

Laryngoscopy and endotracheal intubation markedly stimulate both sympathetic and sympathoadrenal activities, resulting in elevation of blood pressure and tachycardia [1]. Reflex tachycardia and hypertension in response to laryngoscopy and endotracheal intubation are age-old problems encountered by anesthesiologists. Moreover, patients with hypertension are more prone to exhibit an exaggerated hemodynamic response to laryngoscopy and endotracheal intubation [2–5]. Preoperative hypertension has been found to be associated with an increased risk of perioperative tachycardia and hypertension [6]. While the adverse hemodynamic effects of laryngoscopy and endotracheal intubation can precipitate myocardial ischemia, even in patients without hypertension, the responses are exaggerated in patients with hypertension [4, 5].

Many drugs, including opioids and beta-blockers, have been used to modify the hemodynamic response associated with laryngoscopy and tracheal intubation [7–11]. Fentanyl is one of the most useful drugs for preventing these potentially detrimental hemodynamic changes [12, 13]. Large doses (>50 μg/kg) of fentanyl attenuate the detrimental hemodynamic changes by abolishing the catecholamine response to tracheal intubation [13]. Although moderate doses (6–10 μg) of fentanyl can also prevent the detrimental hemodynamic changes during induction of anesthesia, it takes several hours for the fentanyl blood concentration to decrease below the threshold that suppresses spontaneous breathing, and thus the respiratory depressant effects associated with moderate doses can persist beyond the analgesic effects of this drug by two- to threefold [12]. Hence, it is preferable to use relatively small doses of fentanyl (2–5 μg/kg) in order to prevent detrimental hemodynamic changes during induction of anesthesia without causing any respiratory depression. Although there have been some reports showing the effects of small doses of fentanyl on hemodynamic changes during the induction of anesthesia [12–16], there are very few reports examining the effects of small doses of fentanyl on cardiac output.

The present prospective, double-blinded study compared the effects of fentanyl on hemodynamics, catecholamine release and cardiac output in response to endotracheal intubation in patients with and without hypertension.

Methods

All protocols used in this study were approved by the Institutional Review Board of the hospital, and informed consent was obtained from all patients prior to enrolment. Subjects with ASA physical status I or II scheduled to undergo elective general surgical, urological or gynecological procedures under general anesthesia were included in this study.

Patients who were ASA physical status III, IV or V, patients who had an atrioventricular conduction block greater than first degree and patients with a history of drug allergy were excluded from the study. Additional exclusion criteria were history of asthma, bronchospasm, chronic obstructive pulmonary disease, coronary artery disease, heart rate <50 beats/min and systolic blood pressure <80 mmHg at the time of entry into the operation room, active liver disease (glutamine oxaloacetate transaminase or glutamine pyruvate transaminase >50 U/dL), renal dysfunction (plasma creatinine level ≥2.0 mg/dL), cerebrovascular disease and psychiatric illness.

The 45 patients without hypertension and 45 patients with hypertension (total 90 patients) were randomly divided into three groups and scheduled to receive either saline (control), 2.0 μg/kg fentanyl or 4.0 μg/kg fentanyl. The choice of drug treatment was determined using a random number table. All investigators were blinded to the study drug.

Patients without hypertension were defined as individuals who had never been diagnosed as being hypertensive on medical examinations. Patients with hypertension were defined as those taking oral anti-hypertensive medication at the time of their admission to the hospital. In addition, all hypertensive patients selected were controlled hypertensives at the time of hospital admission, with normal blood pressure levels (systolic blood pressure below 139 mmHg) as a result of treatment with anti-hypertensive drugs. Patients with uncontrolled hypertension were excluded from this study due to the possibility that these patients would require additional anti-hypertensive drugs during the induction of anesthesia, which could possibly confound the results. Patients with uncontrolled hypertension were defined as those with elevated blood pressure levels (systolic blood pressure above 160 mmHg) despite treatment with anti-hypertensive drugs at the time of hospital admission [8]. None of the patients with hypertension were receiving beta-blockers. For all the patients with hypertension, anti-hypertensive drug therapy was administered on the morning of surgery. No pre-anesthetic medication, such as sedatives and atropine, were administered to the patients.

After patient arrival in the operating room, an arterial catheter was inserted for continuous monitoring of both arterial blood pressure and cardiac output using the Flo Trac/Vigileo system™ (Edwards Lifesciences, Irvine, CA, USA). Bispectral index (BIS) (version 3.0; Aspect Medical Systems, Newton, MA) was measured continuously on an electroencephalographic monitor (model A-2000; Aspect Medical Systems) using a BIS Sensor strip (Aspect Medical Systems). Impedance of each electrode was maintained at <2 kΩ.

After baseline measurements were recorded under awake conditions, anesthesia was induced with intravenous target-controlled infusion (TCI) of propofol (plasma concentration, 4.0 μg/mL). Rocuronium (0.9 mg/kg) was infused after loss of consciousness. Patients' lungs were ventilated with 100 % oxygen for 120 s, at which time one of the three drugs (saline, 2.0 μg/kg fentanyl or 4.0 μg/kg fentanyl) was administered over 5 s, 2 min after anesthetic induction. Laryngoscopy and tracheal intubation were performed 4 min after induction by an anesthesiologist who was blind to treatment group allocation (Fig. 1). Anesthesia was maintained with a TCI of propofol (4 μg/mL) while breathing 50 % oxygen for 10 min after intubation. End-tidal CO_2 concentrations were maintained at 35–40 mmHg. No other stimulation, such as repositioning or preparing of patients, was permitted during the 10-min

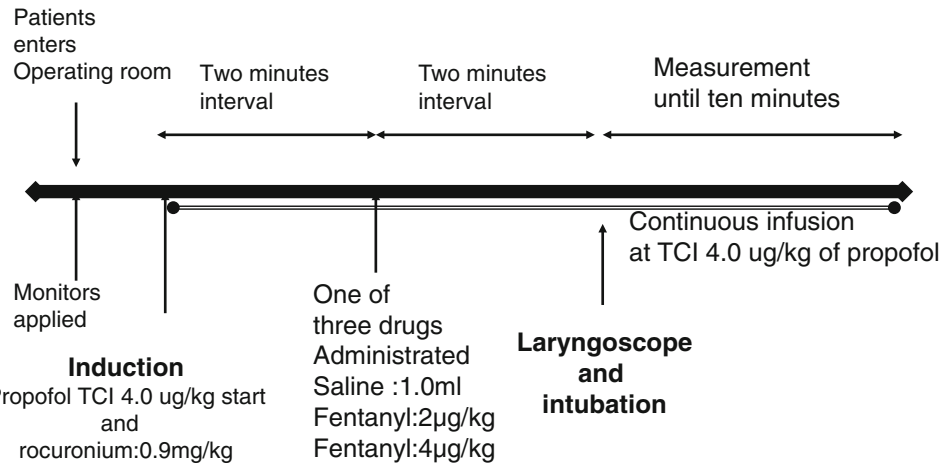

Fig. 1 Schematic diagram of this study protocol

observation period, at which time the study protocol was completed.

Serum epinephrine (E), norepinephrine (NE) and cortisol concentrations were measured during the awake state and 10 min after tracheal intubation. Blood samples were immediately centrifuged and the plasma was separated and stored at −30 °C until assayed. Plasma catecholamine concentrations were measured by the technique of high-pressure liquid chromatography.

Statistical analysis

Data were analyzed at a later time by an individual who was also blind to the treatment regimens.

Before the start of this study protocol, we calculated sample size. Based on a previous study [8], we hypothesized that MAP in the 2 μg/kg fentanyl group would decrease by 12 mmHg compared with that in the control group in patients without hypertension. We determined that 15 members in each group were required to provide an 80 % power to detect a 20 % difference between 2 μg/kg fentanyl and control groups.

All data are expressed as means ± standard deviation (SD). Following the confirmation of equal variance among the groups by the Bartlett test, changes in mean values of heart rate, systolic blood pressure and mean blood pressure (baseline and between groups) were compared using one-way factorial measure or two-way repeated measure ANOVA. When the F value was significant, the Bonferroni method was used for multiple comparisons. Demographic data of the four groups were analyzed by one-way repeated measure ANOVA. As BIS at baseline was 96–99 for all patients, all other BIS values were compared only with post-induction BIS values. Values of $p < 0.05$ were considered statistically significant. All calculations were performed on a Macintosh computer (Apple Co., USA) using SPSS software (SPSS, Chicago, IL, USA) and StatView 5.0 software (Abacus Concepts, Berkeley, CA, USA).

Results

Table 1a, b show the characteristics of the three groups without and with hypertension. There were no significant differences in age, height and weight among the three groups in patients with and without hypertension.

Table 2a, b show the time course of changes in hemodynamic variables in patients without and with hypertension. In patients without hypertension (Table 2a), heart rate (HR) remained unchanged throughout the study period. Mean arterial pressure (MAP) in all three groups decreased before intubation compared with that in the awake period. MAP in the control group increased immediately after intubation. There was a significant difference in MAP among the three groups 2 min after intubation, and MAP decreased 4 min after intubation compared with that in the

Table 1 Characteristics of the three groups without hypertension (a) and with hypertension (b)

	Control	Fentanyl 2 μg/kg	Fentanyl 4 μg/kg	p Value
(a)				
Number	15	15	15	
Age (years)	65 ± 9	63 ± 9	60 ± 13	0.58
Height (cm)	161 ± 8	157 ± 7	164 ± 6	0.22
Weight (kg)	57 ± 6	54 ± 8	59 ± 10	0.46
(b)				
Number	15	15	15	
Age (years)	67 ± 7	64 ± 6	66 ± 6	0.74
Height (cm)	160 ± 8	157 ± 7	159 ± 9	0.80
Weight (kg)	57 ± 10	56 ± 8	59 ± 9	0.84
Anti-hypertensive agents				
Ca channel blocker	8	8	7	
Beta-blocker	6	7	7	
ACE inhibitor	4	4	3	

Ca calcium, *ACE* angiotensin converting enzyme

Table 2 Time course of changes in hemodynamic and BIS variables in patients without hypertension (a) and with hypertension (b)

	1	2	3	4	5	6	7	8	9	10
(a)										
HR (beats/min)										
Control	72 ± 7	66 ± 8	64 ± 11	84 ± 10	80 ± 13	75 ± 10	72 ± 9	70 ± 9	69 ± 9	68 ± 9
Fenta 2	75 ± 6	69 ± 10	67 ± 12	79 ± 10	78 ± 15	76 ± 13	72 ± 9	71 ± 8	68 ± 7	65 ± 8
Fenta 4	75 ± 10	73 ± 6	71 ± 9	76 ± 14	74 ± 11	73 ± 9	71 ± 10	71 ± 9	70 ± 10	68 ± 8
MAP (mmHg)										
Control	100 ± 14	86 ± 21	77 ± 14*	122 ± 17*,#	110 ± 15#	97 ± 10#	84 ± 9#	79 ± 9*	76 ± 10*	73 ± 9*
Fenta 2	98 ± 10	80 ± 17	69 ± 8*	103 ± 18	88 ± 14	82 ± 15	72 ± 9*	68 ± 7*	64 ± 5*	64 ± 4*
Fenta 4	94 ± 12	75 ± 12	64 ± 10*	74 ± 13*,**	70 ± 14*,**	67 ± 13*,**	62 ± 11*	61 ± 11*	60 ± 10*	57 ± 8*
CI (L/min/m^2)										
Control	3.2 ± 0.6	2.5 ± 1.0	2.3 ± 0.5*	4.6 ± 1.8	4.4 ± 1.4	3.1 ± 1.0	2.4 ± 0.4*	2.2 ± 0.4*	2.3 ± 0.4*	2.3 ± 0.6*
Fenta 2	3.1 ± 0.3	2.3 ± 0.5*	2.1 ± 0.2*	3.6 ± 0.8	3.3 ± 1.1	3.0 ± 1.1	2.3 ± 0.5*	2.1 ± 0.2*	2.0 ± 0.2*	2.1 ± 0.2*
Fenta 4	3.3 ± 0.7	2.2 ± 0.8*	1.9 ± 0.5*	2.6 ± 0.6**	2.5 ± 0.9**	2.4 ± 0.9*	2.1 ± 0.7*	2.0 ± 0.5*	2.0 ± 0.4*	1.9 ± 0.3*
SVI (mL/m^2)										
Control	44 ± 11	38 ± 14	36 ± 7*	53 ± 17	52 ± 16	41 ± 10	34 ± 7	32 ± 6	34 ± 6	35 ± 8
Fenta 2	42 ± 7	33 ± 6*	32 ± 5*	47 ± 8	42 ± 7	39 ± 7	32 ± 5	29 ± 3*	28 ± 3*	32 ± 5*
Fenta 4	45 ± 11	29 ± 10*	28 ± 7*	36 ± 6**	33 ± 11**	32 ± 9	30 ± 7	29 ± 5*	29 ± 5*	29 ± 6*
BIS value										
Control	96 ± 1	51 ± 7*	48 ± 5*	49 ± 6*	48 ± 7*	46 ± 8*	42 ± 5*	42 ± 4*	40 ± 7*	41 ± 8*
Fenta 2	96 ± 2	49 ± 4*	44 ± 5*	45 ± 3*	44 ± 4*	43 ± 3*	42 ± 3*	42 ± 4*	41 ± 3*	42 ± 5*
Fenta 4	96 ± 1	48 ± 3*	47 ± 4*	45 ± 9*	45 ± 9*	43 ± 7*	43 ± 7*	43 ± 7*	43 ± 7*	41 ± 5*
(b)										
HR (beats/min)										
Control	75 ± 5	70 ± 5	73 ± 10	98 ± 15*	97 ± 15*	91 ± 12*	84 ± 9	78 ± 9	76 ± 8	71 ± 6
Fenta 2	73 ± 9	69 ± 10	65 ± 9	89 ± 15*	88 ± 12*	80 ± 11	75 ± 8	72 ± 7	69 ± 3	66 ± 6
Fenta 4	76 ± 15	68 ± 10	66 ± 10	75 ± 13#	74 ± 12**,#	71 ± 18	68 ± 14	66 ± 12	65 ± 12	63 ± 9*
MAP (mmHg)										
Control	120 ± 12	82 ± 12*	74 ± 6*	144 ± 19*	135 ± 31	123 ± 25	105 ± 19	97 ± 15	88 ± 15*	80 ± 11*
Fenta 2	121 ± 7	87 ± 15*	76 ± 12*	135 ± 26	130 ± 31	111 ± 29	95 ± 22	86 ± 15*	80 ± 14*	77 ± 14*
Fenta 4	120 ± 15	79 ± 16*	70 ± 3*	82 ± 11*,#	86 ± 16*,#	82 ± 12*,#	79 ± 10*	78 ± 10*	72 ± 8*	68 ± 3*
CI (L/min/m^2)										
Control	3.1 ± 0.3	2.2 ± 0.2*	2.1 ± 0.1*	6.0 ± 0.7*	5.6 ± 1.1*	4.6 ± 0.9*	3.8 ± 1.0	3.1 ± 0.9	2.8 ± 0.7	2.4 ± 0.5*
Fenta 2	3.5 ± 0.6	2.7 ± 0.8	2.1 ± 0.4*	4.9 ± 1.2*	5.2 ± 1.1*	4.1 ± 1.1	3.2 ± 0.9	2.7 ± 0.6	2.5 ± 0.4*	2.4 ± 0.3*
Fenta 4	3.0 ± 0.4	2.1 ± 0.3*	1.9 ± 0.3*	2.8 ± 0.3#	3.1 ± 0.7#	2.9 ± 0.7#	2.5 ± 0.3	2.3 ± 0.2*	2.1 ± 0.2*	2.0 ± 0.2*
SVI (mL/m^2)										
Control	40 ± 4	32 ± 5	31 ± 5*	62 ± 8*	56 ± 7*	48 ± 7	42 ± 10	37 ± 8	36 ± 7	34 ± 5
Fenta 2	42 ± 7	38 ± 7	31 ± 6*	55 ± 8*	59 ± 7*	50 ± 10	42 ± 8	38 ± 8	35 ± 5	37 ± 4
Fenta 4	39 ± 3	33 ± 8	31 ± 6*	43 ± 4#	43 ± 4#	39 ± 3#	36 ± 4	34 ± 4	34 ± 4	33 ± 4*
BIS value										
Control	96 ± 1	49 ± 4*	46 ± 2*	45 ± 2*	44 ± 2*	43 ± 3*	42 ± 3*	41 ± 3*	40 ± 3*	40 ± 3*
Fenta 2	97 ± 2	50 ± 3*	45 ± 4*	44 ± 4*	44 ± 4*	42 ± 4*	41 ± 5*	41 ± 3*	40 ± 4*	40 ± 5*
Fenta 4	96 ± 3	48 ± 5*	43 ± 4*	42 ± 4*	41 ± 4*	42 ± 4*	42 ± 5*	42 ± 4*	41 ± 4*	41 ± 4*

Data are expressed as mean ± SD. Fenta 2: fentanyl 2 μg/kg group, Fenta 4: fentanyl 4 μg/kg group

1: awake, 2: after induction of anesthesia, 3: before intubation, 4: immediately after intubation, 5: one min after intubation, 6: two min after intubation, 7: three min after intubation, 8: four min after intubation, 9: five min after intubation, 10: ten min after intubation

HR heart rate, *MAP* mean arterial pressure, *CI* cardiac index, *SVI* stroke volume index, *BIS* bispectral index

* $p < 0.05$ compared with time point 1, ** $p < 0.05$ compared with Fenta 2 group at same time point, # $p < 0.05$ compared with other groups

awake period, the decrease lasting up to 10 min after intubation. Cardiac index (CI) and stroke volume index (SVI) in all three groups decreased before intubation compared with that in the awake period. Decreased CI or SVI returned to awake values after intubation in all three groups, although there was a significant difference in CI or SVI between the 4 μg/kg fentanyl group and the other two groups immediately and 1 min after intubation. CI decreased 3 min after intubation in all three groups, the decrease lasting for 10 min after intubation.

In the patients with hypertension (Table 2b), HR in the control and 2 μg/kg fentanyl groups increased after

Table 3 Changes in plasma epinephrine, norepinephrine and cortisol levels between the pre- and post-induction period in patients without (a) and with hypertension (b)

	Pre-induction	10 min after intubation
(a)		
Epinephrine (pg/mL)		
Control	48 ± 23	25 ± 9
Fentanyl 2 μg/kg	58 ± 24	6 ± 4*,#
Fentanyl 4 μg/kg	49 ± 25	5 ± 1*,#
Norepinephrine (pg/mL)		
Control	112 ± 23	59 ± 25*
Fentanyl 2 μg/kg	141 ± 37	51 ± 23*
Fentanyl 4 μg/kg	156 ± 70	66 ± 47*
Cortisol (μg/dL)		
Control	11 ± 2	8 ± 3
Fentanyl 2 μg/kg	13 ± 2	11 ± 2
Fentanyl 4 μg/kg	15 ± 3	11 ± 2
(b)		
Epinephrine (pg/mL)		
Control	165 ± 37	81 ± 38*
Fentanyl 2 μg/kg	131 ± 79	47 ± 39*
Fentanyl 4 μg/kg	152 ± 67	10 ± 4*, #
Norepinephrine (pg/mL)		
Control	235 ± 78	133 ± 21*
Fentanyl 2 μg/kg	213 ± 64	99 ± 36*
Fentanyl 4 μg/kg	238 ± 62	35 ± 15*, #
Cortisol (μg/dL)		
Control	13 ± 4	10 ± 4
Fentanyl 2 μg/kg	12 ± 4	11 ± 3
Fentanyl 4 μg/kg	19 ± 10	12 ± 8

Data are expressed as mean ± SD

* $p < 0.05$ compared with pre-induction. # $p < 0.05$ compared with control

intubation. MAP in all three groups decreased before intubation compared with that in the awake period. A differential time course of changes in MAP was observed among the three groups after intubation. CI in the three groups decreased after the induction of anesthesia and increased after intubation in the control and 2 μg/kg fentanyl groups compared with that in the awake period. SVI in the three groups also decreased after the induction of anesthesia and increased after intubation in the control and 2 μg/kg fentanyl groups compared with that in the awake period.

Table 3a, b show the changes in epinephrine (E), norepinephrine (NE) and cortisol concentrations in patients without and with hypertension between the pre- and post-induction periods. E and NE concentrations decreased significantly after the induction of anesthesia in all three groups in patients both with and without hypertension. In patients without hypertension, E concentration in both the 2 and 4 μg/kg fentanyl groups decreased 10 min after intubation, with no difference between the 4 μg/kg fentanyl and 2 μg/kg fentanyl groups 10 min after intubation. In patients with hypertension, E and NE concentrations in the 4 μg/kg fentanyl group significantly differed from that in the control and 2 μg/kg fentanyl groups 10 min after intubation.

Discussion

The present study shows that: [1] administration of 2 μg/kg fentanyl minimizes the hemodynamic changes in patients without hypertension, preventing the increases in HR, MAP and cardiac output associated with tracheal intubation; and [2] administration of 4 μg/kg fentanyl minimizes the hemodynamic changes in patients with hypertension, preventing the increases in HR, MAP and cardiac output associated with tracheal intubation.

Numerous previous studies have been published regarding prevention of the abrupt hemodynamic changes associated with tracheal intubation [2, 7–16]. In clinical practice, beta-blockers [10, 11], calcium antagonists [8] and lidocaine [15] are often used to prevent the hemodynamic changes, as are fentanyl, remifentanil, sufentanil and inhaled anesthetics [12–17]. Abrupt hemodynamic changes during induction of anesthesia and tracheal intubation increase the risk of myocardial ischemia, especially in predisposed patients, such as those with hypertension. In patients with hypertension, larger doses of fentanyl, remifentanil, sufentanil and inhaled anesthetics are needed to prevent the hemodynamic changes as compared to patients without hypertension, because of the exaggerated, albeit transient, sympathetic response in patients with hypertension following noxious stimuli such as laryngoscopy [2, 8, 9, 14]. Although many researchers have examined the effects of these agents on stabilization of BP and HR during the induction of anesthesia and tracheal intubation, simultaneous maintenance of adequate cardiac output is also important. However, few reports have examined the alterations in cardiac output during induction of anesthesia and tracheal intubation [7, 8, 12]. Miller et al. [7] examined the dose-related effects of alfentanil on HR, BP and cardiac output responses to tracheal intubation and showed that alfentanil caused cardiac output to remain unchanged for 7 min in the post-intubation period. In a previous study [8], we examined the effects of propofol (1 mg/kg), landiolol (0.1 mg/kg) and nicardipine (1 mg) on the changes in cardiac output due to endotracheal intubation, and showed that administration of landiolol (0.1 mg/kg) and nicardipine (1 mg) 2 min before intubation effectively stabilized cardiac output in the post-intubation period in patients

without hypertension. Van Aken et al. [12] examined the effects of propofol combined with fentanyl (3 μg/kg) on hemodynamic changes during tracheal intubation, and found that the combination of fentanyl and propofol depressed cardiac output before and after tracheal intubation. They [12] also reported that additional administration of 3 μg/kg of fentanyl resulted in a further significant decrease in arterial pressure and cardiac output after induction of anesthesia compared with that without additional fentanyl, in patients without hypertension receiving 70 % nitrous oxide/propofol anesthesia. Our study shows that in regard to stabilizing hemodynamics and cardiac output during anesthetic induction and tracheal intubation, 2 μg/kg fentanyl is adequate in patients without hypertension, while 4 μg/kg fentanyl is required in patients with hypertension to prevent the hemodynamic changes associated with tracheal intubation.

In this study, plasma E and NE significantly decreased 10 min after intubation in both patients with and without hypertension, even in the control group. However, despite the decreases in plasma E and NE concentrations with administration of a TCI of 4.0 μg/mL of propofol in the control group, the lower concentrations of E and NE were not enough to stabilize the hemodynamic changes 10 min after intubation. In addition, the amount of decrease in the concentrations of E and NE differed from each other. This differential decrease in the concentrations of E and NE might be partially responsible for the alteration in hemodynamics 10 min after intubation. Baseline concentrations of E and NE in hypertensive patients were two- to threefold higher than those in patients without hypertension. This could in part explain the larger fentanyl dose requirement for stabilization of hemodynamics after the induction of anesthesia in patients with hypertension. There was no relationship between the maximal decrease in cardiac output or MAP after the induction of anesthesia and the decrease in plasma E or NE 10 min after intubation in patients both with and without hypertension among the three groups (data not shown). Thus, solely preventing the elevation of E and NE could not avoid the abrupt hemodynamic changes observed 10 min after intubation. The anesthetic agents used for induction, baseline sympathetic activity level or baseline hormone level such as renninangiotensin, may all modulate the hemodynamic changes 10 min after intubation.

Study limitations

First, the use of different combinations and dosages of anesthetic agents, such as thiopental, propofol, etomidate, ketamine and midazolam, greatly influence hemodynamic changes during the induction of anesthesia. The propofol TCI method is used for induction of anesthesia and can easily maintain anesthetic depth, as assessed by BIS. A recent review [23] showed that TCI technology is becoming a routine anesthesia technique for the practitioner, rather than a research tool for specialists and those who are enthusiasts of intravenous anesthesia; hence, we selected the propofol TCI method for induction of anesthesia in our study.

Another concern of this study is that we used fentanyl rather than remifentanil to stabilize hemodynamics. Remifentanil, an ultra-short-acting opiate that is widely available in Japan, has been shown to stabilize hemodynamics during anesthetic induction. The infusion rate of remifentanil can be easily controlled, thus minimizing the abrupt hemodynamic changes associated with anesthetic induction, while simultaneously eliminating the need for fentanyl. However, adverse hemodynamics, such as severe bradycardia and cardiac arrest, has been observed after the administration of remifentanil [18, 19]. In addition, shivering after anesthesia occurs more frequently in patients treated with remifentanil than in those treated with fentanyl [20]. Recently, IV-PCA (patient-controlled analgesia) using fentanyl is widely used for postoperative analgesia in Japan. Hence, some physicians prefer to use fentanyl instead of remifentanil during the induction of anesthesia [21]. Hence, we opted to use fentanyl in this study.

Patients with hypertension receive a variety of antihypertensive drugs, so that it is possible that the magnitude of hemodynamic changes during induction of anesthesia depends on the kind of antihypertensive medication. However, most of the hypertensive patients in this study were treated with a combination of anti-hypertensive drugs (Table 1b). We did not find any difference in the magnitudes of hemodynamic changes during intubation in hypertensive patients treated with the different antihypertensive drug combinations (data not shown).

Finally, it is of concern whether the Flo Trac system^{R} can precisely reflect cardiac output during periods of abrupt hemodynamic changes, such as those occurring during the induction of anesthesia. However, Fukuda [22] reported that cardiac output measured by the latest Flo Trac system software (Ver. 3.02) used in this study showed the highest degree of precision compared with that measured by pulmonary artery catheters, even during abrupt hemodynamic changes.

In this study, plasma E and NE concentrations were measured 10 min after the induction of anesthesia. Ours [8] and other previous [1, 3] reports showed that it takes several minutes for plasma catecholamine concentrations to achieve a steady state after the induction of anesthesia.

In conclusion, our study shows that administration of 2 μg/kg fentanyl in patients without hypertension and 4 μg/kg fentanyl in patients with hypertension minimizes

the changes in heart rate, systolic blood pressure and cardiac output associated with tracheal intubation under 4.0 μg/mL propofol TCI anesthesia.

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