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Effects of fentanyl on cardiovascular and plasma catecholamine responses in surgical patients

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Abstract
Purpose. Whether opioids administered before skin incision, under inhalational anesthesia, improve cardiovascular and plasma catecholamine responses to surgical stimulation compared with those administered after skin incision remains unclear. We compared the effects of fentanyl injected before and after skin incision on these responses.
Methods. We studied 50 healthy female patients [American Society of Anesthesiologist (ASA) physical status 1] who underwent elective total abdominal hysterectomy through an infraumbilical incision (midline incision) under nitrous oxide (60%)–oxygen–isoflurane (1.2%) anesthesia. Fentanyl (2.0 or 4.0 μg·kg^{-1}) was administered IV 5 min before (pretreatment group) or 5 min after (posttreatment group) skin incision. Control patients received a saline injection. Heart rate (HR) and mean arterial blood pressure (MAP) were recorded 1 min before incicsion and serially for 30 min afterward. Plasma levels of norepinephrine (Nor) and epinephrine (Epi) were determined 1 min before incision and serially up to 20 min after skin incision.
Results. The MAP response to incision had decreased after 10 min in posttreatment fentanyl (2 μg·kg^{-1}) ($P < 0.05$) and after 8, 10, 15, and 20 min in posttreatment fentanyl (4 μg·kg^{-1}) ($P < 0.05$). At the same doses, fentanyl administered before skin incision attenuated MAP response to incision after 1 min with the smaller dose ($P < 0.05$) and after 1, 3, 5, 6, 8, 10, 15, and 20 min with the higher dose ($P < 0.05$). Fentanyl suppressed Epi response to surgery 8 and 20 min after skin incision ($P < 0.05$) at both doses, except for 8 min after incision in pretreatment fentanyl (2 μg·kg^{-1}). Overall, the hemodynamic and sympathoadrenergic responses after skin incision were attenuated, with the exception of plasma Nor after fentanyl irrespective of time and dose.
Conclusions. Our results indicated that fentanyl depressed cardiovascular and plasma catecholamine responses irrespective of the time of administration, and that the higher dose of fentanyl produced a greater suppression of MAP and HR responses. In addition, the depressant effects on MAP of high-dose fentanyl administered 5 min before skin incision lasted longer than when injected 5 min after incision. At both doses, the opioid attenuated the rise in plasma Epi, but not Nor.

Key words Fentanyl · Catecholamine · Cardiovascular responses · Surgery

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Introduction

The response to surgical noxious stimulation includes changes in both the cardiovascular system and plasma catecholamine concentrations [1–4]. Roizen et al. [1] reported the dose–response effects of anesthetics on blockade of the autonomic response to skin incision, defining the minimum alveolar concentration to block the adrenergic response (MAC–BAR) as the concentration of halothane or enflurane required to block the adrenergic reaction to skin incision in 50% of patients. Subsequently, Daniel et al. [2] reported the dose–response effects of isoflurane on MAC–BAR with and without fentanyl (MAC–BAR of 1.8%). In contrast, Zbinden et al. [3] reported that isoflurane (0.6–1.8 vol%) alone did not cause a dose-related attenuation of the response of blood pressure and heart rate to skin incision, but they studied relatively few patients at above 1.8%. Moreover, Segawa et al. [4] reported that the effects of isoflurane on norepinephrine response to surgical noxious stimulation were inversely proportional to the dose, although the cardiovascular responses to such stimuli were depressed in a concentration-dependent manner. Thus, it has been well established that a combination of volatile anesthetics and opioids, such as fentanyl and morphine, attenuates the hemodynamic and adrenergic responses to surgical stimulation. However, only few studies have compared the effects of intravenously administered (IV) opioids on surgery-induced cardiovascular and catecholamine responses before skin incision with those of inhalational

anesthesia alone after skin incision, although there are many reports on postoperative pain such as preemptive analgesia [5–7].

In this study, we examined the effects of IV fentanyl, administered either before or after skin incision, on cardiovascular and catecholamine responses to surgical noxious stimulation. The studies were conducted on patients who were all subjected to the same surgical procedure, and included measurements of plasma levels of epinephrine (Epi) and norepinephrine (Nor).

Methods

After approval by the Committee on Human Research at our institutions and with informed consent of the patients, we undertook a prospective, randomized study of 50 healthy (ASA physical status 1) women. All were scheduled for elective total abdominal hysterectomy through an infraumbilical incision (midline incision) to treat myoma uteri. We selected patients who would remain in the lithotomy position for surgery. The patients had fasted for 12 h before entering the operating room.

All patients were premedicated with an intramuscular injection of atropine sulfate (0.5 mg) 30 min before entering the operating room. They were divided at random into five groups, and fentanyl (2.0 or 4.0 $\mu g \cdot kg^{-1}$) was administered intravenously either 5 min before (pretreatment group) or 5 min after (posttreatment group) abdominal incision. Saline was used as the placebo at both times (5 min before and after incision) in the control group. A catheter was inserted into the left antecubital vein for infusion of lactated Ringer's solution at a rate of 10 $ml \cdot kg^{-1} \cdot h^{-1}$ at 9 A.M.

Prior to anesthesia, electrocardiographic (ECG) monitoring and oxygen saturation monitoring were established for each patient. An automated system to measure blood pressure (noninvasive; BP 508; Nippon Colin, Aichi, Japan) was placed on the right arm and set to cycle and record at 1-min intervals for the duration of the study. The system also monitored the heart rate (HR), the concentration of inhaled anesthetic agent, expired CO_2 concentration, and body temperature. The concentration of the anesthetic inspired was calibrated before each study with a standard gas.

Once three successive readings at 1-min intervals of HR and mean blood pressure (MBP) varied by less than 10%, 100% oxygen was delivered by a facemask. Three minutes later, anesthesia (thiamylal, an ultrashort-acting barbiturate, 5 $mg \cdot kg^{-1}$; succinylcholine, 1 $mg \cdot kg^{-1}$) was injected intravenously. After tracheal intubation, the lungs were ventilated mechanically with nitrous oxide (60%), oxygen, and isoflurane (1.2%). Paralysis was maintained with vecuronium bromide (0.1 $mg \cdot kg^{-1}$), which was administered 10 min before skin incision. Lactated Ringer's solution was infused at a rate of 10 $ml \cdot kg^{-1} \cdot h^{-1}$. After an equilibration period of at least 15 min at 1.2% isoflurane, HR and mean arterial blood pressure (MAP) were recorded 1 min before skin incision. They were also recorded 1, 3, 5, 6, 8, 10, 15, 20, 25, and 30 min after skin incision. There were 10 women in each group, and 1 min before skin incision and 3, 8, and 20 min after skin incision, 4 ml of blood was withdrawn from an indwelling peripheral venous catheter in the dorsum of the right hand. Arterial blood gases were analyzed and blood sugar level was determined 30 min after incision. At the same time, plasma concentrations of Epi and Nor were determined by high-pressure liquid chromatography (HPLC).

Samples to determine plasma concentrations of Epi and Nor were centrifuged in a refrigerated centrifuge as soon as possible after collection. The resultant plasma was stored at −20°C prior to analysis. Plasma Epi and Nor concentrations were determined by HPLC.

Statistical analysis

Data are presented as means ± SEM. Fisher's least-significant difference procedure, with Bonferroni's adjustment, was used for multiple comparisons. A P value less than 0.05 was considered to be statistically significant.

Results

All studies were performed between 1:00 P.M. and 8:00 P.M. The patients in all five groups were similar in terms of age, weight, height, arterial PCO_2, arterial PO_2, dose of thiamylal at induction of anesthesia, preinduction HR, preinduction MAP, and body temperature at skin incision (Table 1). In all patients, blood loss during the study was less than 30 ml including blood samples. The blood sugar levels ranged from 90 to 110 $mg \cdot dl^{-1}$. At 1 min before skin incision, MAP, HR, and plasma concentrations of Epi and Nor were similar among all five groups.

Cardiovascular responses

Measurements were made prior to the induction of anesthesia, 1 min before skin incision, and 1, 3, 5, 6, 8, 10, 15, 20, 25, and 30 min after skin incision (time 0) (Figs. 1, 2). Maximum MAP after skin incision on fentanyl (2 $\mu g \cdot kg^{-1}$) in the control, pretreatment, and posttreatment groups were 121, 149, and 120 mmHg, respectively. Minimum MAP after skin incision on fentanyl (2 $\mu g \cdot kg^{-1}$) in the control, pretreatment, and posttreatment groups were 68, 68, and 64 mmHg, respectively.

Table 1. Patient demographics

	Control	Pretreatment fentanyl ($2\,\mu g \cdot kg^{-1}$)	Posttreatment fentanyl ($2\,\mu g \cdot kg^{-1}$)	Pretreatment fentanyl ($4\,\mu g \cdot kg^{-1}$)	Posttreatment fentanyl ($4\,\mu g \cdot kg^{-1}$)
Age (years)	44.5 ± 0.9	46.8 ± 1.3	42.5 ± 0.9	45.9 ± 1.4	45.7 ± 1.7
Height (cm)	156.0 ± 1.6	152.6 ± 1.3	156.2 ± 2.1	154.7 ± 1.7	157.2 ± 1.9
Weight (kg)	56.4 ± 2.7	53.4 ± 2.2	57.5 ± 2.1	53.9 ± 3.2	58.4 ± 2.3
Dose of thiamylal at induction (mg)	240 ± 16.8	265.0 ± 25.1	268.8 ± 14.0	255.6 ± 19.6	247.2 ± 13.5
Body temperature at skin incision (°C)	36.6 ± 0.1	36.6 ± 0.1	36.5 ± 0.1	36.5 ± 0.2	36.5 ± 0.2
Arterial CO_2 (mmHg)	36.2 ± 0.7	34.6 ± 0.1	34.2 ± 1.4	34.5 ± 1.2	35.3 ± 1.2
Pre-induction HR (b.p.m.)	91.4 ± 5.5	92.9 ± 7.6	91.1 ± 4.8	92.6 ± 3.2	90.0 ± 5.2
Pre-induction MAP (mmHg)	108.4 ± 4.9	106.0 ± 3.7	102.9 ± 4.7	108.8 ± 3.7	99.6 ± 4.3

Mean ± SE ($n = 10$ in each group)

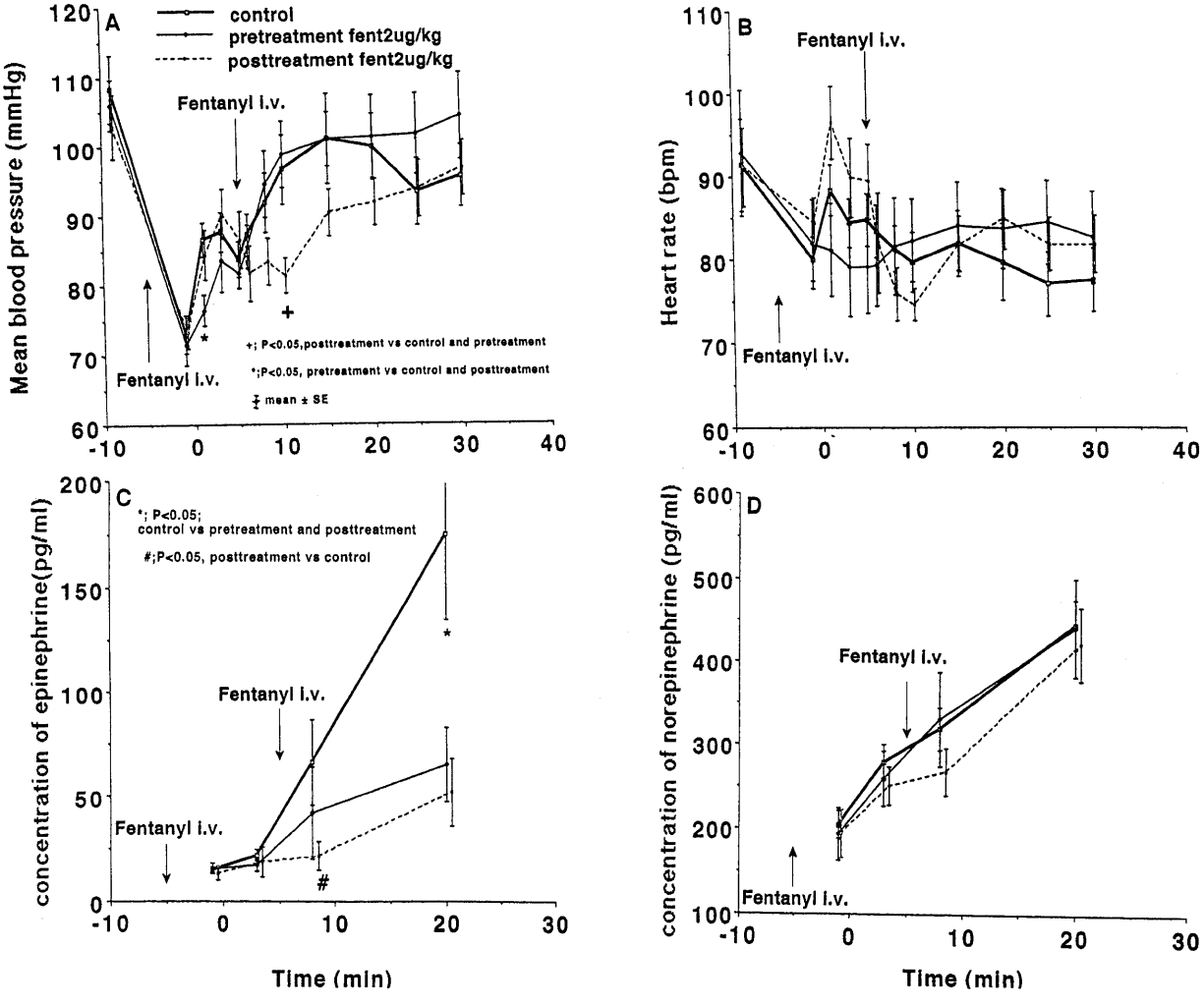

Fig. 1. Effects of $2\,\mu g \cdot kg^{-1}$ fentanyl on cardiovascular and catecholamine responses. **A** Mean blood pressure, and **B** heart rate. **C** Epinephrine, and **D** norepinephrine

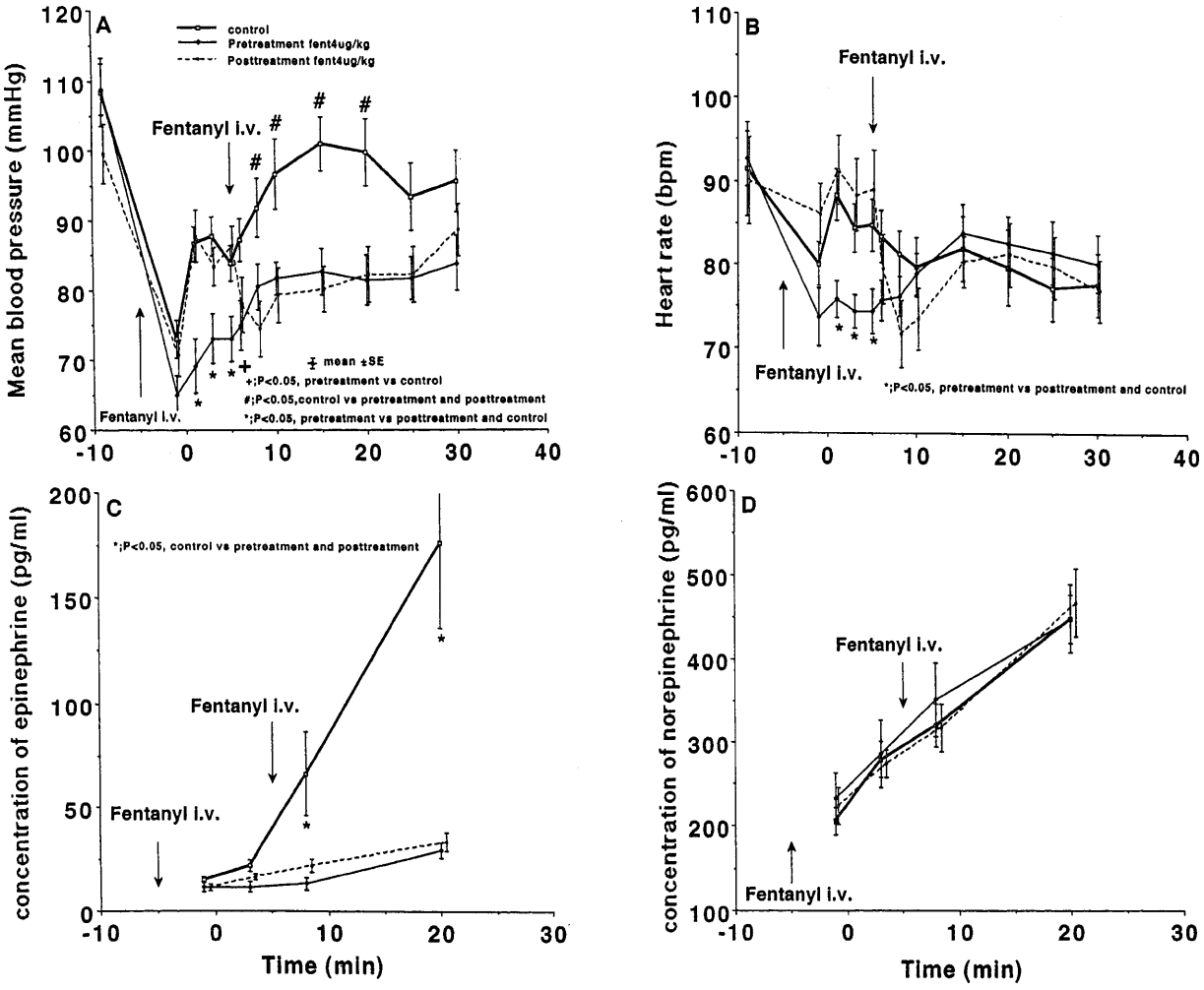

Fig. 2. Effects of 4 μg·kg^{-1} fentanyl on cardiovascular and catecholamine responses. **A** Mean blood pressure, and **B** heart rate. **C** Epinephrine, and **D** norepinephrine

Maximum MAP after skin incision on fentanyl (4 μg·kg^{-1}) in the control, pretreatment, and posttreatment groups were 121, 104, and 110 mmHg, respectively. Minimum MAP after skin incision on fentanyl (4 μg·kg^{-1}) in the control, pretreatment, and posttreatment groups were 68, 53, and 60 mmHg, respectively.

Maximum HR after skin incision on fentanyl (2 μg·kg^{-1}) in the control, pretreatment, and posttreatment groups were 108, 110, and 118 b.p.m., respectively. Minimum HR after skin incision on fentanyl (2 μg·kg^{-1}) in the control, pretreatment, and posttreatment groups were 62, 50, and 58 b.p.m., respectively. Maximum HR after skin incision on fentanyl (4 μg·kg^{-1}) in the control, pretreatment, and posttreatment groups were 108, 107, and 110 b.p.m., respectively. Minimum HR after skin incision on fentanyl (4 μg·kg^{-1}) in the control, pretreatment, and posttreatment groups were 62, 53, and 60 b.p.m., respectively. Therefore, there were no life-threatening cardiovascular responses such as hypertension, hypotension, or bradycardia in any patient.

In women in the control group under isoflurane–nitrous oxide anesthesia, who received saline before or after skin incision, we noted significant increases in MAP at each measurement ($P < 0.05$) after incision, and in HR at 1 min ($P < 0.05$) after incision (compared with their preincision MAP and HR).

When fentanyl (2 or 4 μg·kg^{-1}) was administered before skin incision, the MAP response to incision was a decrease at 1 min with fentanyl (2 μg·kg^{-1}) ($P < 0.05$) and at 1, 3, 5, 6, 8, 10, 15, and 20 min with fentanyl (4 μg·kg^{-1}) ($P < 0.05$). When fentanyl (2 and 4 μg·kg^{-1}) was administered after skin incision, the MAP response to incision was a decrease at 10 min with fentanyl (2 μg·kg^{-1}) ($P < 0.05$), and at 8, 10, 15, and 20 min with fentanyl (4 μg·kg^{-1}) ($P < 0.05$). The HR response to incision was a decrease at 1, 3, and 5 min ($P < 0.05$) when fentanyl (4 μg·kg^{-1}) was administered before skin incision. Overall, IV fentanyl (2.0 or 4.0 μg·kg^{-1}) at both 5 min before or 5 min after incision has equivalent blocking effects on cardiovascular

responses, and it reduced these responses in a dose-dependent manner.

Response of plasma catecholamines

Figures 1 and 2 show plasma levels of Epi (C) and Nor (D) 1 min before skin incision and 3, 8, and 20 min after skin incision (time 0). The plasma concentrations of Nor and Epi were significantly higher at 8 and 20 min after skin incision ($P < 0.05$) compared with those at 1 min before skin incision in the control group.

Intravenous fentanyl (2 or 4 $\mu g \cdot kg^{-1}$) in the pre- and posttreatment groups decreased the plasma level of Epi in response to surgery at 8 and 20 min after skin incision ($P < 0.05$) except for 8 min after incision in the pretreatment fentanyl (2 $\mu g \cdot kg^{-1}$) group. The degree of blockade in the Epi response was not significantly different between pre- and posttreatment groups. However, IV fentanyl (2 or 4 $\mu g \cdot kg^{-1}$) showed that there were no significant changes in plasma levels of Nor in response to surgery at any time interval.

Overall, IV fentanyl (2.0 or 4.0 $\mu g \cdot kg^{-1}$) 5 min before or 5 min after incision has equivalent blocking effects on the plasma catecholamine response. Furthermore, fentanyl did not suppress this response in a dose-dependent manner. At the doses tested, opioid attenuated the rise in plasma Epi, but not Nor.

Discussion

Our study showed that intraoperative reactions to surgical stimulation, which include changes in MAP, HR, and plasma levels of Epi, but not Nor, were blocked when the opioid fentanyl (2 and 4 $\mu g \cdot kg^{-1}$) was administered intravenously before and after skin incision. These data, with the exception of the level of Nor, are similar to those of Daniel et al. [2], who reported that 1.5 and 3.0 $\mu g \cdot kg^{-1}$ fentanyl injected intravenously 5 min before the stimulus equivalently decreased by 60%–70% the concentration of isoflurane required to block cardiovascular responses to a skin incision.

The MAC of isoflurane was considered to be 1.15% [8] and that of nitrous oxide 104%. The MAC of isoflurane was assumed to be additive with respect to that of nitrous oxide. We selected 1.6 MAC of isoflurane because we assumed that the ED_{50} of isoflurane to block the adrenergic response to incision (MAC–BAR) might be close to this level, and because we considered that the use of MAC–BAR might abolish or attenuate the stress responses to surgical incision. Since MAC–BAR values for isoflurane had not been reported when we started our study, we extrapolated them from those of enflurane (1.6 MAC) and halothane (1.45 MAC) reported by Roizen et al. [1]. A recent study showed that isoflurane–nitrous oxide (60%) anesthesia with 1.85 MAC corresponded to MAC–BAR [2]. The 1.6 MAC used for isoflurane–nitrous oxide (60%) anesthesia was somewhat lower than 1.85 MAC reported by Daniel et al. [2]. The 1.6 MAC for isoflurane–nitrous oxide anesthesia, which was employed in our study, did not prevent hemodynamic reactions and did not block increases in plasma levels of Epi and Nor at 3, 8, and 20 min after skin incision in any of our patients. Inada et al. [9] reported that isoflurane–nitrous oxide anesthesia with 1.5 MAC failed to suppress the hemodynamic reaction to painful stimuli, which included skin incision. Moreover, Segawa et al. [3] reported that 1.67 MAC isoflurane in oxygen and nitrogen did not block hemodynamic and adrenergic reactions to surgical stimulation. Thus, our data, obtained with isoflurane–nitrous oxide, are compatible with these two studies.

We selected 5 min before and 5 min after skin incision as the time for the administration of fentanyl because fentanyl exerts its analgesic effect from 5 to about 30–60 min [10,11], and the central sensitization has already occurred 5 min after noxious stimulation in animal studies [12]. We expected that the timing of the administration of fentanyl would be important in blocking cardiovascular and sympathoadrenal responses to surgical stimulation. However, the present results showed that IV fentanyl administered before or after incision has an equivalent degree of depresseant effect on cardiovascular and sympathoadrenal responses after skin incision. Posttreatment fentanyl (4 $\mu g \cdot kg^{-1}$) decreased the MAP response for 12 min (from 8 to 20 min after skin incision), in contrast to 20 min (from 1 to 20 min) in pre-treatment fentanyl (4 $\mu g \cdot kg^{-1}$). With regard to the duration of the depressant effect on MAP response after skin incision, pretreatment fentanyl (4 $\mu g \cdot kg^{-1}$) has a longer effect than a posttreatment dose in spite of the rapid decline in the plasma fentanyl level with a smaller dose [13].

It has been reported that isoflurane by itself does not protect against central sensitization [14]. Low doses of opioid prevent central sensitization, while a high dose is required to suppress central sensitization once it has already developed in an animal [15,16]. Thus, it seems appropriate to ensure that adequate opioids are active before the surgical stimulation of a patient under inhalational general anesthesia, with larger doses of opioid, administered after skin incision, being required for an active antinociceptive effect. Thus, in the present study, we confirmed the preemptive antinociceptive effects of fentanyl with respect to the duration of the depressant effect on the MAP response.

Consistent with a previous report [17], our results suggest that intravenous administration of fentanyl after skin incision decreases HR during isoflurane–nitrous oxide anesthesia. However, this decrease in HR was not

significantly different from that in the control group. The reasons for the decrease in HR 5–30 min after skin incision in the control group are complex, but might involve a combination of blockage of the evoked HR response to noxious stimulation and a baroreceptor reflex. In addition, previous studies by Cahalan et al. [17] showed that intravenous fentanyl ($1.0\,\mu g \cdot kg^{-1}$) administered after skin incision decreased MAP during isoflurane anesthesia. Our results confirmed these findings, but in our study the reduction of MAP after fentanyl was only transient, and MAP returned to the basal level within 20 min.

Philbin et al. [18] also reported the lack of any correlation between an increase in MAP and an elevation of plasma concentrations of Epi and Nor under opioid anesthesia. It is possible that not only catecholamines, but also other hormones [19], are involved in the cardiovascular control system. It remains unclear why changes in cardiovascular parameters and plasma levels of catecholamines are not more closely related.

Intravenous fentanyl, administered before and after skin incision, suppressed increases in plasma levels of Epi but not of Nor compared with the control group. Previous studies have confirmed that the greater the dose of anesthetic, the greater the suppression of stimulation-induced response [20]. Moreover, it is well established that a combination of volatile anesthetics and opioids such as fentanyl attenuates hemodynamic and adrenergic reactions to surgical stimulation [1,2]. Therefore, the difference between Epi and Nor in terms of their responses to surgical noxious stimulation was unexpected, because both responses are usually increased by noxious stimulation [21]. However, Klingstedt et al. [22] showed that both high-dose ($100\,\mu g \cdot kg^{-1}$) and low-dose ($5\,\mu g \cdot kg^{-1}$) fentanyl anesthesia failed to suppress increases in the plasma concentration for Nor, and furthermore, that high-dose but not low-dose fentanyl suppressed the increase in plasma Epi concentrations during cholecystectomy. Our results and the report cited indicate that opioids do not necessarily reduce plasma levels of Epi and Nor simultaneously.

High (2.5%–5%), but not low (1.3%), concentrations of isoflurane increase hemodynamic parameters and plasma levels of catecholamines when there is a rapid increase in the concentration of isoflurane, but such changes do not occur in control patients given a fixed concentration of isoflurane [23]. Moreover, the plasma concentration of Nor increases in adults after the induction of anesthesia with thiopental followed by ventilation with isoflurane, nitrous oxide, and oxygen [24]. Within 15 min after induction, the concentration of Nor returns to the preinduction level. To exclude such a phenomenon, we included an equilibration period of at least 15 min at 1.2% isoflurane after the induction of anesthesia. In the present study, MAP was lower 1 min before incision than before the induction of anesthesia. Although we did not measure the plasma concentrations of catecholamines before induction, our results are similar to those of Yil-Hankala et al. [23]. In their study, the plasma concentrations of Epi and Nor were approximately 50 and $250\,pg \cdot ml^{-1}$, respectively, after stable isoflurane (1.3%) anesthesia for 15 min. Vecuronium is known to have few, if any, autonomic effects [25]. However, our results might have been influenced, at least in part, by nitrous oxide, because nitrous oxide is known to augment sympathetic outflow [26] and also decreases the rate of removal of Nor from the pulmonary circulation [27].

All patients received atropine and hydroxyzine as a premedication, and this may explain why the average intraoperative HR was 70–90 in all groups. Atropine impairs the proper evaluation of the vagotonic effects of opioids. Furthermore, hydroxyzine is known to reduce the MAC of halothane [28], and thus may also reduce the MAC of isoflurane. However, atropine and hydroxyzine as a premedication is routinely used in all patients in our hospital, with the exception of patients in whom such drugs are contraindicated.

The secretion of adrenal catecholamines in animals and humans is influenced by changes in the internal environment, such as hemorrhage, hypotension, hypothermia, asphyxia, changes in blood sugar level, and cutaneous stimulation [29]. Increases in plasma levels of catecholamines are also caused by hypercarbia [30]. In our patients, adequate oxygenation and ventilation were provided, as indicated by blood-gas tension, and minimal blood loss occurred during the first 30 min of the surgical procedure. Changes in the factors mentioned above were similar in each group. We terminated our measurements 30 min after skin incision since we could not rule out possible changes in the internal environment later on.

In conclusion, we have demonstrated that IV fentanyl (2.0 or $4.0\,\mu g \cdot kg^{-1}$) given 5 min before or 5 min after skin incision produces similar depressant effects in cardiovascular and plasma catecholamine responses, and that the high-dose fentanyl produced a greater suppression of MAP and HR responses to stimulation. In addition, the duration of the depressant effect on the MAP response after skin incision was longer when fentanyl ($4\,\mu g \cdot kg^{-1}$) was given before, rather than after, treatment. At the doses tested, opioids seem to attenuate the rise in plasma Epi but not Nor.

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