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# Hemodynamic stability during induction of anesthesia and tracheal intubation with propofol plus fentanyl, ketamine, and fentanyl-ketamine

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**Abstract**

*Purpose.* This study was conducted to investigate hemodynamic and cardiac stability during anesthesia induction and intubation, using propofol plus fentanyl, propofol plus ketamine, and propofol plus fentanyl and ketamine.

*Methods.* Forty-five adult patients were randomly allocated to one of three groups according to the agents used for induction: propofol (2 mg/kg) plus fentanyl (3 μg/kg) (PF), propofol (2 mg/kg) plus ketamine (0.1 mg/kg) (PK), and propofol (2 mg/kg) plus fentanyl (3 μg/kg) plus ketamine (0.1 mg/kg) (PFK). Hemodynamic responses were assessed by measuring changes in blood pressure (BP), heart rate (HR), and cardiac output (CO; using dye dilution combined with pulse dye densitometry [PDD]).

*Results.* BP and HR changes during the induction of anesthesia tended to be greater in the PK group than in the PF and PFK groups. After the injection of propofol, the cardiac index (CI) fell significantly below baseline values in the PF and PFK groups, but remained unchanged in the PK group. After tracheal intubation, BP and HR increased significantly only in the PF and PK groups, and reached a level significantly above baseline values only in the PK group. The CO responses to tracheal intubation were: PK group > PF group > PFK group.

*Conclusion.* A combination of propofol plus fentanyl plus ketamine would provide greater reduction of fluctuations in hemodynamic variables associated with induction of anesthesia and tracheal intubation than combinations of propofol plus fentanyl or propofol plus ketamine.

**Key words** Hemodynamics · Propofol · Fentanyl · Ketamine · Pulse dye densitometry (PDD)

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## Introduction

The induction of general anesthesia and tracheal intubation can have significant hemodynamic consequences, and many strategies have been used for limiting these. Propofol is widely used for the induction of anesthesia. However, the recommended dose for intravenous bolus induction, 2.5 mg/kg, may induce a considerable degree of hypotension prior to intubation but may not suppress the hypertensive responses to laryngoscopy and tracheal intubation [1]. The addition of fentanyl to the propofol used for induction has been recommended as a way of decreasing the hypertensive response to intubation, but, unfortunately, fentanyl can increase the preintubation hypotension [1,2]. Ketamine has been advocated as an anesthetic agent for poor-risk patients on account of its safety and because of the favorable effects upon cardiovascular functions that result from its sympathomimetic properties [3,4]. In fact, a high degree of hemodynamic stability can be achieved by using a combination of ketamine and propofol, while a combination of propofol, fentanyl, and ketamine has been used for total intravenous anesthesia [5]. However, there are no studies in the literature that have compared the hemodynamic changes that occur during the induction of anesthesia and tracheal intubation in patients given propofol together with fentanyl, propofol together with ketamine, and propofol together with both these agents.

Assessment of the hemodynamic changes accompanying the induction of anesthesia and tracheal intubation is usually confined to the measurement of changes in heart rate (HR) and blood pressure (BP). In the present study, we also measured cardiac output (CO), by means of dye dilution combined with pulse dye densitometry (PDD), which has been introduced as a new method for determining CO [6]. We compared the hemodynamic responses that occurred when anesthesia was induced by three methods: propofol plus

fentanyl, propofol plus ketamine, and propofol plus fentanyl plus ketamine.

## Subjects and methods

The 45 patients studied were American Society of Anesthiologists (ASA) physical status 1 or 2, aged 40–65 years, and were undergoing general anesthesia for surgical procedures; 25 were men and 20 were women. The study protocol was approved by our Institutional Human Investigation Committee, and written informed consent was obtained from each patient on the day before surgery. The patients were randomly allocated in a double-blind fashion to one of three groups according to the agents to be used for the induction of anesthesia: propofol-fentanyl (PF) ($n$ = 15; 9 men and 6 women), propofol-ketamine (PK) ($n$ = 15; 6 men and 9 women), or propofol-fentanyl-ketamine (PFK) ($n$ = 15; 10 men and 5 women). We excluded patients in whom one or more of the following disease states were present: hypertension, and coronary artery, respiratory, renal, or cerebral disease.

All patients were premedicated with intramuscular hydroxyzine 50 mg 1 h before the study began. When the patient arrived in the operating room, an intravenous cannula (20 G) was inserted, under local anesthesia, and Ringer's solution was administered, at 10 ml/kg per h throughout the study period. Blood pressure (BP) was monitored via an automated BP cuff. Monitoring by electrocardiograph and pulse oximetry was also established. Intermittent measurements of cardiac output (CO) were made by the indocyanine green dye-dilution method [6].

Measurements of pre-induction BP, HR, and CO were used as baseline values. The patients in the PF group received fentanyl 3 μg/kg, followed 60 s later by propofol 2 mg/kg and saline 0.2 ml/kg. The patients in the PK group received 3 ml of saline, followed 60 s later by propofol 2 mg/kg and ketamine 0.1 mg/kg. The patients in the PFK group received fentanyl 3 μg/kg, followed 60 s later by propofol 2 mg/kg and ketamine 0.1 mg/kg. Vecuronium 0.1 mg/kg was given as a rapid intravenous bolus to facilitate tracheal intubation, which was performed 4–5 min after induction. The patients' lungs were manually ventilated for 4 min with 100% oxygen before orotracheal intubation was performed. Direct laryngoscopy was carried out using a Macintosh blade, and tracheal intubation was accomplished within 30 s. The patients' lungs were then mechanically ventilated with a tidal volume of 10 ml/kg and a respiratory rate of 12/min to maintain end-tidal $PaCO_2$ at around 38 mmHg. Anesthesia was maintained with propofol 6 mg/kg per h supplemented with 50% nitrous oxide in oxygen.

### *Data recording*

In each patient, BP and HR were recorded at 1-min intervals for 3 min after the induction of anesthesia, with the initial response to tracheal intubation being taken as the levels reached in the first minute after the beginning of laryngoscopy. Cardiac output (CO) and stroke volume (SV) were measured at three time-points: baseline (3 min before induction of general anesthesia), preintubation (3 min after induction), and postintubation (3 min after tracheal intubation).

Data values are expressed as means ± SD. Mean blood pressure (MBP) was taken as diastolic blood pressure (DBP) plus 1/3 × (systolic blood pressure [SBP]-DBP). Statistical comparisons among the groups were performed using two-way analysis of variance (ANOVA), followed by an unpaired $t$-test with Bonferroni's correction. Hemodynamic responses to induction and intubation in a given group were analyzed using a repeated-measurements ANOVA (one-way ANOVA) followed by a paired $t$-test with Bonferroni's correction. A value of $P < 0.05$ was considered the minimum level of statistical significance.

## Results

The patients in all three groups were similar in terms of age and body weight, and in terms of baseline values of BP and HR (Table 1).

### *Induction of general anesthesia*

In all three groups of patients, BP fell immediately after the injection of propofol, whether or not fentanyl and/or ketamine were also injected, but the BP level tended to remain higher in the PK group than in the PF and PFK groups (Fig. 1a). Heart rate (HR) decreased in the PF and PFK groups, but in the PK group it was increased as early as 1 min after induction (Fig. 1b). There was no significant difference, in terms of the BP and HR responses to induction, between the PF and PFK groups. At 3 min after induction, CO and the cardiac index (CI) were significantly lower than baseline in the PF and PFK groups, but they remained unchanged in the PK group (Table 1 and Fig. 2b). The cardiac index (CI) decreased significantly, by 10% ($P < 0.05$), in the PF group, and by 12% ($P < 0.05$) in the PFK group. At the preintubation time-point, the stroke volume index (SVI) remained unchanged in all groups (Fig. 2a).

### *Tracheal intubation*

The increases in MAP and HR above the preintubation levels were significant only in the PF and PK groups,

**Table 1.** Hemodynamic data at three time-points (3 min before [baseline] and 3 min after induction of anesthesia [preintubation], and 3 min after tracheal intubation [postintubation])

| | Baseline | | | Preintubation | | | Postintubation | | |
|---|---|---|---|---|---|---|---|---|---|
| | PK | PF | PFK | PK | PF | PFK | PK | PF | PFK |
| SBP | 130 ± 16 | 134 ± 17 | 133 ± 16 | 110 ± 14* | 102 ± 13* | 96 ± 11* | 125 ± 21** | 110 ± 20** | 103 ± 12 |
| DBP | 74 ± 9 | 77 ± 10 | 77 ± 9 | 64 ± 9* | 57 ± 9* | 54 ± 7* | 71 ± 14** | 61 ± 13** | 57 ± 7 |
| HR | 69 ± 11 | 71 ± 11 | 71 ± 8 | 73 ± 13* | 67 ± 11* | 64 ± 8* | 83 ± 12** | 70 ± 11 | 67 ± 8 |
| CO | 4.5 ± 1.2 | 5.1 ± 1.4 | 4.8 ± 1.3 | 4.5 ± 1.4 | 4.4 ± 1.2* | 4.0 ± 0.8* | 6.1 ± 1.7** | 5.2 ± 1.3** | 4.4 ± 1.1 |
| CI | 3.0 ± 0.8 | 3.2 ± 0.9 | 3.1 ± 0.9 | 3.0 ± 0.9 | 2.8 ± 0.7* | 2.5 ± 0.4* | 4.0 ± 1.1** | 3.3 ± 0.6** | 2.8 ± 0.6 |
| SV | 65 ± 14 | 68 ± 23 | 67 ± 19 | 61 ± 17 | 66 ± 21 | 64 ± 18 | 72 ± 15** | 72 ± 19 | 66 ± 15 |
| SVI | 43 ± 8 | 43 ± 14 | 43 ± 11 | 41 ± 13 | 44 ± 13 | 41 ± 9 | 48 ± 10** | 45 ± 11 | 42 ± 7 |

* $P < 0.01$ versus baseline; ** $P < 0.01$ versus preintubation
Values are expressed as means ± SDs
PK, Propofol + ketamine; PF, propofol + fentanyl; PFK, propofol + fentanyl + ketamine; SBP, systolic arterial pressure; DBP, diastolic arterial pressure; HR, heart rate; CO, cardiac output; CI, cardiac index; SV, stroke volume

and the levels reached were significantly above baseline only in the PK group (Fig. 1a,b). The CO response to tracheal intubation (postintubation time-point) was greater in the PK group than in the PF and PFK groups (Table 1). The tracheal intubation maneuver (which lasted 30 s) caused CI to increase above the preintubation level by 35% ($P < 0.05$) in the PK group and by 20% in the PF group ($P < 0.05$). The postintubation level of CI was significantly higher in the PK group than in the PF or PFK groups ($P < 0.05$; Fig. 2b), the rank order being PK > PF > PFK. At the postintubation time-point in the PFK group, CO, CI, SV, and SVI remained unchanged compared with their preintubation levels. Stroke volume index showed no response to tracheal intubation in the PF and PFK groups, but increased significantly in the PK group (Fig. 2a).

## Discussion

In the present study, anesthesia with propofol plus fentanyl plus ketamine provided excellent protection against fluctuations in hemodynamic and cardiac variables at the time of tracheal intubation. Propofol plus ketamine did suppress hemodynamic and cardiac functions after induction, but it failed to prevent the cardiovascular responses to laryngoscopy and tracheal intubation.

Fentanyl is added to the propofol used for induction as a way of decreasing the hypertensive response to laryngoscopy and tracheal intubation. In a previous study, when given with propofol 2.4 or 2.5 mg/kg, fentanyl (2 or 3 μg/kg) decreased the amplitude of the BP response to intubation [1]. However, the administration of fentanyl with propofol can increase the preintubation hypotension. Thus, Billard et al. [2] reported that the mean decrease in systolic BP after 2 mg/kg propofol was 28 mmHg when no fentanyl was given, but 53 mmHg or 50 mmHg, respectively, when 2 μg/kg or 4 μg/kg of fentanyl was added. In their study [2], the hemodynamic changes seen after induction with propofol or propofol plus fentanyl were not altered when the propofol dose was increased from 2 to 3.5 mg/kg. In the present study, a decrease in systolic pressure of about 32 mmHg was observed after induction with propofol plus fentanyl (2 mg/kg and 3 μg/kg, respectively).

Ketamine has been recommended for poor-risk patients on account of its safety and because of the favorable effects upon cardiovascular functions that result from its sympathomimetic properties [3]. The signs of its cardiovascular stimulation include increases in HR, CI, and arterial pressure [3,4]. In a previous study, a combination of propofol and ketamine was found to provide stable hemodynamics, by comparison with the lowered blood pressure found in patients given propofol and fentanyl [5]. In that study, anesthesia was induced with propofol (2 mg/kg) and either fentanyl (3 μg/kg) or ketamine (1 mg/kg). These doses of propofol and fentanyl are the same as those used in the present study. In the present study, the BP and HR responses to induction with propofol plus ketamine tended to be higher than those seen with propofol plus fentanyl. When ketamine was added to propofol plus fentanyl, for the purpose of preventing hypotension after induction, the hemodynamic response was similar to that seen with propofol plus fentanyl.

We measured CO by pulse-dye densitometry (PDD), using indocyanine green (ICG). PDD is a minimally invasive technique, compared with the thermodilution method, which requires the insertion of a pulmonary arterial catheter. This newly developed technique measures CO by determining the pulse concentration of ICG in the peripheral arterial blood. Imai et al. [6] reported that, with PDD, CO could be measured repeatedly with the same degree of accuracy as with the thermodilution method.

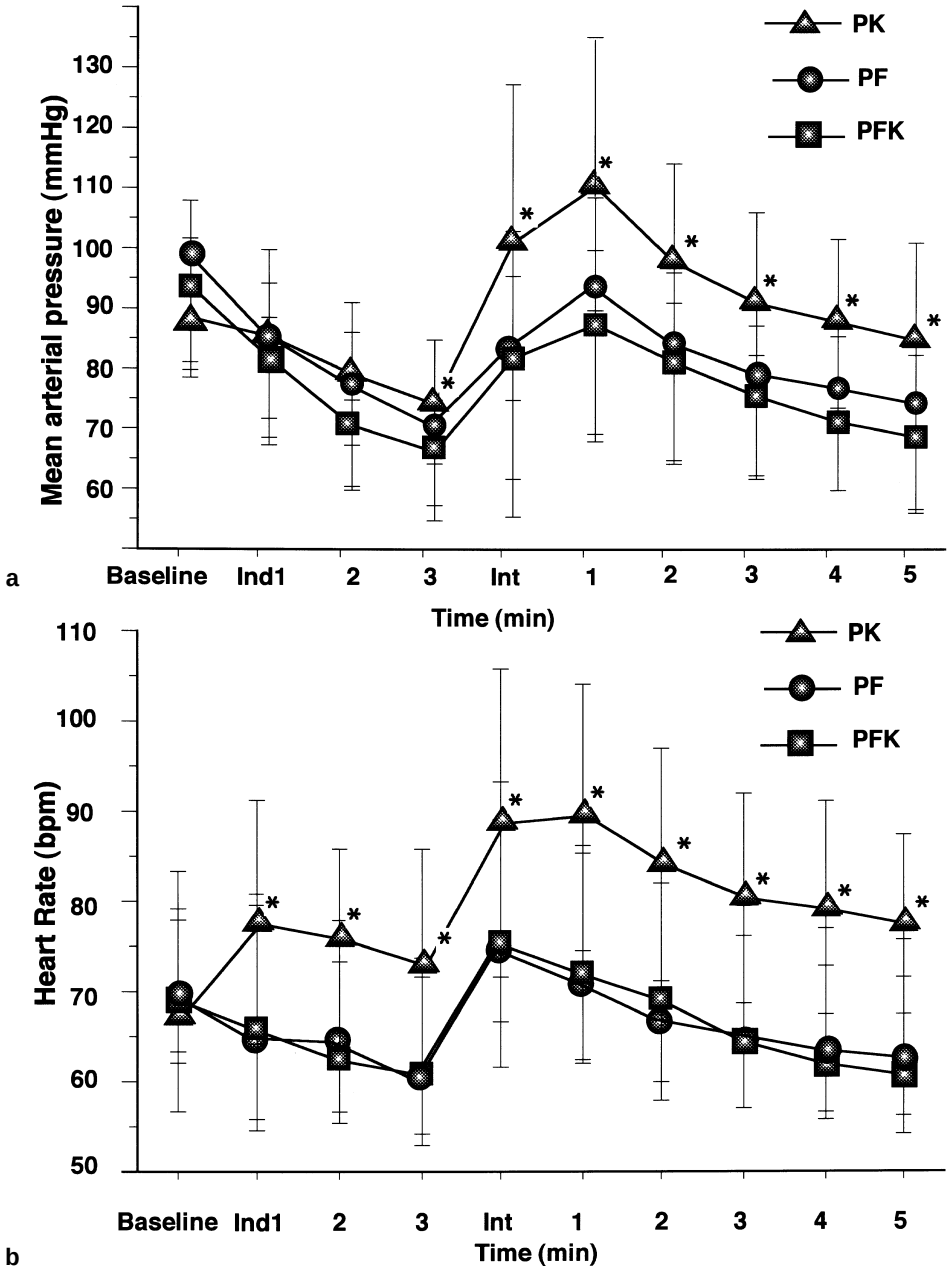


**Fig. 1. a** Changes in mean arterial pressure and **b** heart rate after the induction of anesthesia and tracheal intubation. Anesthesia was induced with propofol plus fentanyl (PF; *round symbols*), propofol plus ketamine (PK; *triangular symbols*), or propofol plus fentanyl plus ketamine (PFK; *square symbols*). Data values are expressed as means ± SDs. $*P < 0.05$ compared with baseline values. *Ind*, Induction; *int*, intubation

In the present study, with propofol plus fentanyl or propofol plus fentanyl plus ketamine the CO values obtained after induction were significantly lower than the baseline values. Lepage et al. [7] reported that propofol 2 mg/kg (alone or in combination with fentanyl 5 μg/kg) did not alter left ventricular performance in patients with good left ventricular function. With the PDD method, SVR cannot be measured directly. However, when fentanyl (5 μg/kg) was given with propofol (2 mg/kg), induction was associated with a decrease in blood pressure caused exclusively by decreases in CI and SVRI [7]. Ketamine has been reported to produce an increase in CO, and heart rate [3,4]. By one of several mechanisms, ketamine induces both the direct stimulation of medullary cardiovascular centers and indirect sympathomimetic effects produced by the blockade of catecholamine reuptake. Induction with propofol plus ketamine prevents the suppression of hemodynamic and cardiac functions normally seen after induction with propofol alone. In the present study, tracheal intubation caused CO to increase in patients given propofol plus ketamine, possibly because the stimula-

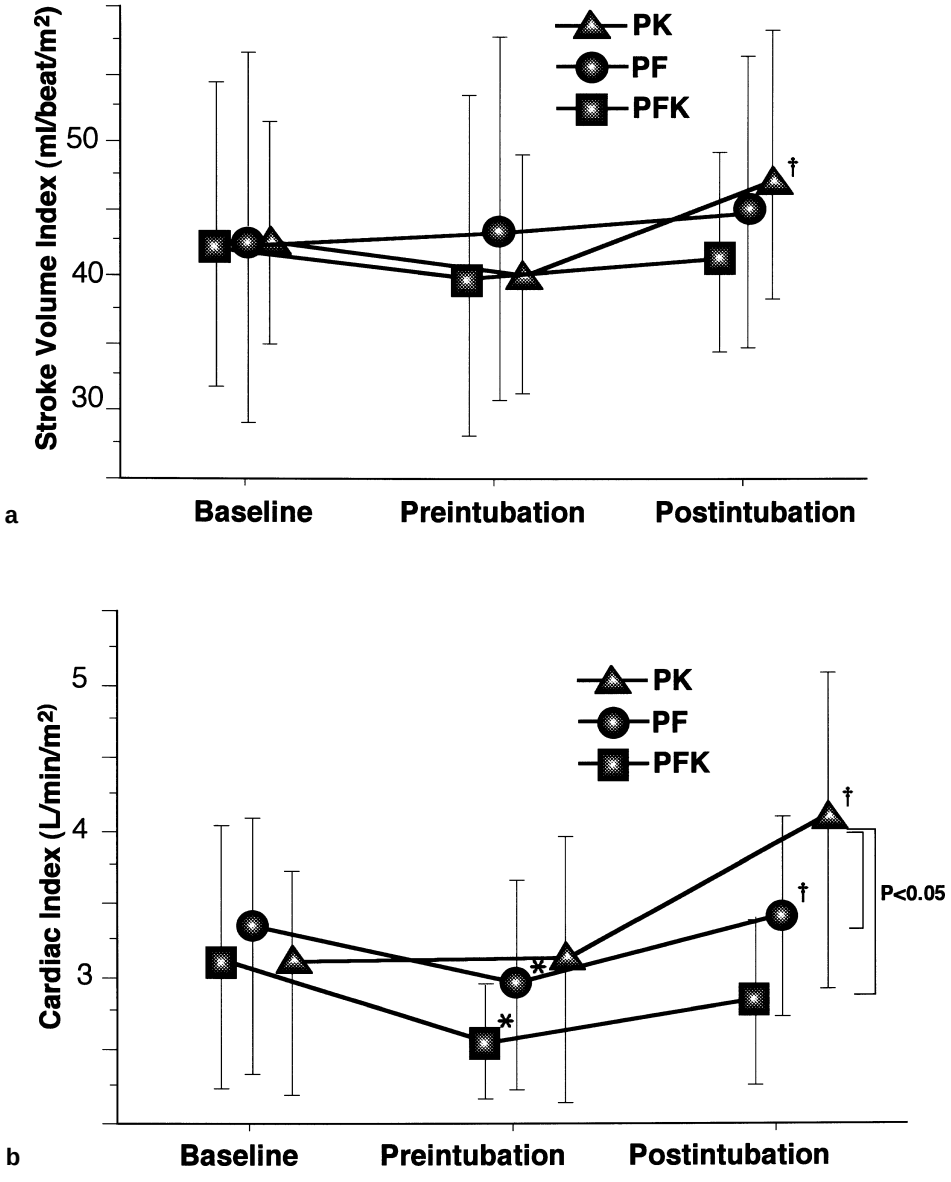


**Fig. 2. a** Changes in stroke volume index and **b** cardiac index after the induction of anesthesia and tracheal intubation. Anesthesia was induced with propofol plus fentanyl (PF; *round symbols*), propofol plus ketamine (PK; *triangular symbols*), or propofol plus fentanyl plus ketamine (PFK; *square symbols*). Data values are expressed as means ± SDs. $^{*}P < 0.05$ compared with baseline value; $^{\dagger}P < 0.05$ compared with preintubation value. *Baseline*, 3 min before inductions of anesthesia; *preintubation*, 3 min after induction; *postintubation*, 3 min after tracheal intubation

tion of HR and myocardial function resulting from sympathomimetic tracheal intubation were enhanced by the sympathomimetic effects of ketamine. A smaller, but significant, increase in CO was seen after intubation when propofol plus fentanyl was used. However, the cardiac and BP responses to tracheal intubation were less with propofol plus fentanyl plus ketamine than with either propofol plus fentanyl or propofol plus ketamine. These results show that the addition of fentanyl to propofol plus ketamine suppressed the stimulatory effects of ketamine on cardiovascular functions. In previous studies, when the sympathetic tone was abolished; for example, during general anesthesia with halothane and enflurane or during epidural anesthesia, ketamine produced no pressor response [8,9]. Thus, it would appear that the effects of ketamine administration on circulation dynamics may differ between general anesthesia and the conscious state. In the present study, it is possible that the administration of fentanyl could have attenuated the cardiovascular stimulation caused by ketamine.

With anesthetics, cardiovascular dynamics change to an extent that depends both on the dose of the anesthetic and on the time of administration of the anesthetic. Ben-Shlomo et al. [10] examined dose-response data for propofol plus fentanyl, using bootstrap and isobolographic analysis. The median effective dose (ED50) values (for no response to verbal command)

were 0.95 mg/kg for propofol and 1.9 μg/kg for fentanyl (given in combination). When a combination of ketamine and propofol was used in a different study, ED50 values of 0.63 mg/kg for propofol and 0.21 mg/kg for ketamine were obtained (to achieve hypnosis) [11]. This dose of ketamine is considerably lower than that used in the present study, as well as being considerably lower than the doses used in the other studies mentioned above, and might be expected to have a comparatively small effect on cardiovascular dynamics. In the present study, patients were tracheally intubated 5–6 min after the injection of fentanyl and 4–5 min after the injection of propofol. These time intervals may represent the approximate times required to reach peak effect for each drug [2,12].

In conclusion, the results of the present study show that the induction of anesthesia with propofol plus fentanyl plus ketamine provides a somewhat greater degree of protection against fluctrations in hemodynamic variables than propofol plus fentanyl, and a considerably greater degree of protection than propofol plus ketamine. The administration of fentanyl at the time of induction may suppress the sympathetic nervous system and attenuate the cardiovascular stimulation caused by ketamine.

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