J Anesth (1999) 13:77–82

Journal of Anesthesia

© JSA 1999

# Comparative effects of etomidate, ketamine, propofol, and fentanyl on myocardial contractility in dogs

Atsushi Kawakubo[1], Toru Fujigaki[2], Hiroyuki Uresino[2], Shiping Zang[2], and Koji Sumikawa[2]

[1] Department of Anesthesia, Hamamatsu Medical Center, 328 Tomizuka, Hamamatsu, Shizuoka 432-8002, Japan
[2] Department of Anesthesiology, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

**Abstract**
*Purpose.* The present study was carried out to determine the direct effects of etomidate, ketamine, propofol, and fentanyl on myocardial contractility, and whether fentanyl would enhance the myocardial depression caused by propofol.
*Method.* The anesthetics were injected directly into the circuit that supplied blood to the left circumflex coronary artery (LCX) in anesthetized open-chest dogs. Myocardial contractility was evaluated from measurements of percent segmental shortening (%SS).
*Results.* Etomidate, ketamine, and propofol significantly reduced %SS in a dose-dependent manner. The %SS values with 1.6 and 3.2 mg of etomidate were similar to those with 3.2 and 6.4 mg of ketamine, respectively, and the %SS value with 6.4 mg of propofol was similar to those with 3.2 and 6.4 mg of ketamine. Fentanyl alone had no effects on myocardial performance and did not influence the effect of propofol on %SS.
*Conclusion.* On the basis of clinical doses, the direct myocardial depressant effect of ketamine is more than twice as potent as that of etomidate and slightly more than that of propofol. Fentanyl has no inotropic effect and does not enhance the direct myocardial depressant effect of propofol.

**Key words:** Intravenous anesthetics, Etomidate, Ketamine, Propofol, Fentanyl, Myocardial contractility

## Introduction

The induction of general anesthesia with propofol is associated with a considerable decrease in arterial blood pressure [1]. Although fentanyl alone is reported to produce minimal changes in hemodynamic values [2], the combination of propofol and fentanyl resulted in further decreases in arterial blood pressure, heart rate, and cardiac output as compared with propofol alone [3]. On the other hand, the induction of general anesthesia with ketamine produces cardiovascular stimulation [4], and etomidate produces minimal cardiovascular depression [5]. These responses would result from overall effects on cardiac function, preload, systemic resistance, and autonomic and central nervous system activity, and would be altered by the condition of the patients and the simultaneous administration of other drugs. Therefore, knowledge of the direct effects of anesthetic agents on myocardial contractility would be important for anesthesia in critically ill patients.

It is difficult to assess the direct effects of agents in vivo because of concomitant changes in preload, systemic resistance, and autonomic and central nervous system activity. Direct intracoronary injections of small doses of agents using the extracorporeal perfusion system minimize systemic effects, and this method is suitable to determine the direct effects of agents on myocardial contractility in vivo. Some investigators have used this system to evaluate the direct cardiac effects of agents, including local anesthetics [6] and propofol [7]. However, there have been no comparative studies of intravenous anesthetics.

The present study was carried out to determine the direct effects of etomidate, ketamine, propofol, and fentanyl on myocardial contractility, and whether fentanyl would enhance the myocardial depression caused by propofol.

## Materials and methods

The study was approved under the Guidelines of Animal Experimentation at Nagasaki University. Twenty mongrel dogs of either sex weighing 11–15 kg were studied, 8 for the first study and 12 for the second study. Approximately 1 h after sedation with 2.5 mg·kg$^{-1}$ of morphine sulfate subcutaneously, each dog was anesthetized with an intravenous bolus injection of alfa-

*Address correspondence to*: A. Kawakubo
Received for publication on June 22, 1998; accepted on October 14, 1998

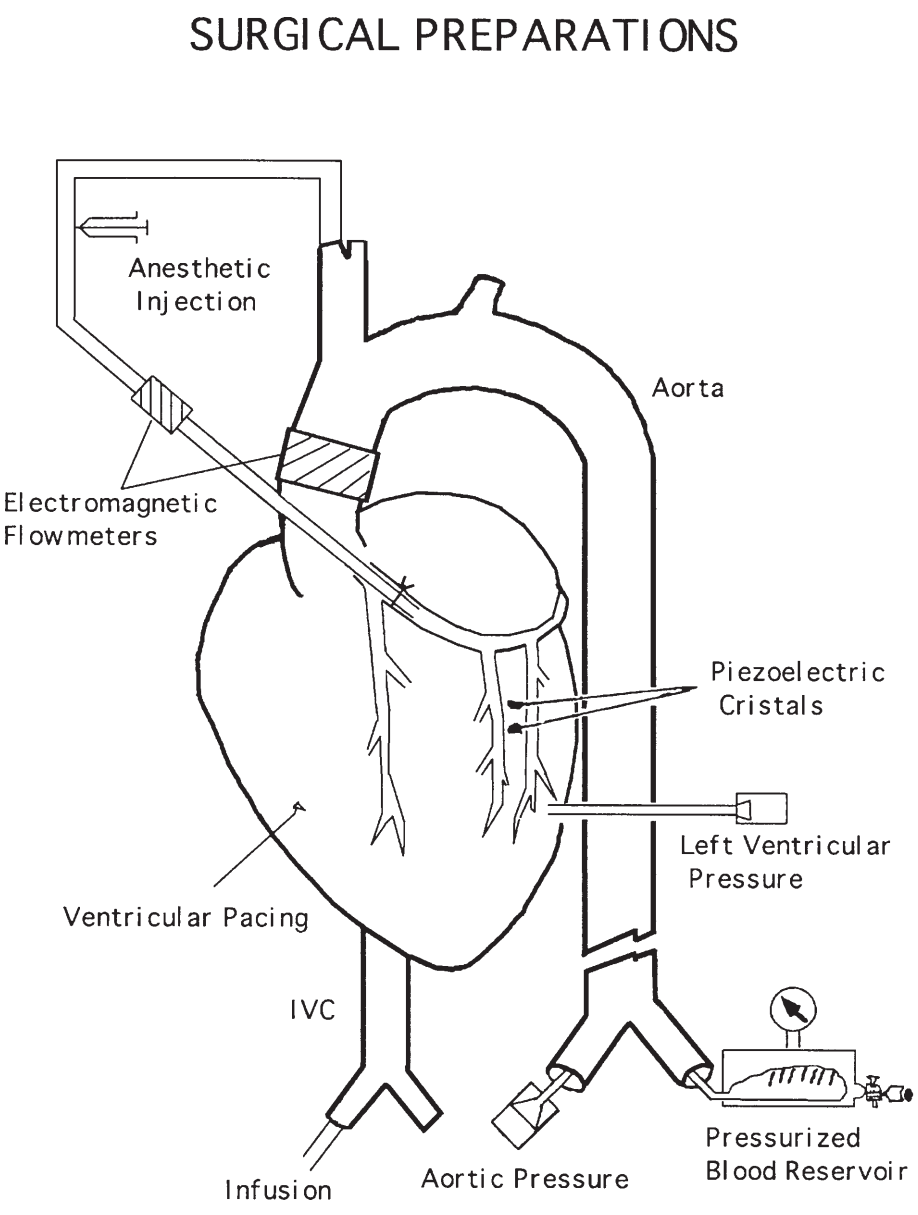


**Fig. 1.** Surgical preparations

chloralose at a dose of 100 mg·kg$^{-1}$. Anesthesia was maintained with continuous intravenous infusion of alfa-chloralose at a rate of 10 mg·kg$^{-1}$·h$^{-1}$, and neuromuscular blockade was maintained with pancuronium bromide 4 mg i.v. Isoflurane was inhaled only during placement of the equipment. After tracheal intubation, the lungs of each dog were mechanically ventilated with oxygen with a volume ventilator (Harvard). End-tidal $CO_2$ was monitored continuously with a gas analyzer (Capnomac Ultima; Datex, Helsinki, Finland) and was maintained between 30 and 35 mmHg. Esophageal temperature was maintained between 36.5 and 37.5°C with a heating lamp.

Surgical preparations are shown in Fig. 1. Each 7F polyethylene catheter was inserted into the abdominal aorta via the right femoral artery to measure arterial blood pressure, the abdominal aorta via the left femoral artery for the control of arterial blood pressure using a pressurized blood reservoir, the carotid artery for an external perfusion circuit, and the left femoral vein for infusion. Lactated Ringer's solution was administrated at a rate of 10 ml·kg$^{-1}$·h$^{-1}$. Sodium bicarbonate was given as appropriate to correct metabolic acidosis. Blood coagulation in the extracorporeal circuit was prevented by an intravenous injection of sodium heparin at a dose of 750 U·kg$^{-1}$.

The left chest was entered through the fifth intercostal space, and the heart was suspended in a pericardial cradle. Cardiac output (CO) was measured by an electromagnetic flowmeter (MFX-2100; Nihon Koden,

Tokyo, Japan) placed on the ascending aorta. Formalin was injected into the region of the A–V node to produce a complete block of A–V conduction. Thereafter the heart rate was controlled at 100 bpm by ventricular pacing. Mean arterial pressure (MAP) was controlled at 80 mmHg by using a pressurized blood reservoir connected to the left femoral artery. A stainless-steel cannula was inserted into the LCX 2 cm distal from its origin, followed by ligation of its proximal site. Arterial blood from a carotid artery was supplied to this cannula by an extracorporeal perfusion circuit. LCX blood flow (CXF) was measured with an electromagnetic flowmeter (MFX-2100) located in this circuit. The total volume of the extracorporeal perfusion circuit was 15 ml, and the partial volume from the injection port to the LCX was 7 ml. A catheter-tip transducer (PT-157; Goodman, Nagoya, Japan) was inserted into the left ventricle to measure left ventricular pressure continuously, and the maximum rate of increase of left ventricular pressure (LVdP/dt) was calculated.

A pair of piezoelectric crystals was implanted 7–10 mm apart in the myocardium of the area supplied by the LCX to a depth approximately midway between the epicardium and the endocardium. This area was defined by injection of 3 ml of India ink into the cannula at the end of the experiment. The myocardial segment length between the implanted crystals was measured continuously with an ultrasonic dimension unit (NEC-Sanei, Tokyo, Japan). End-systolic length (ESL) was determined at the maximum negative left ventricular dP/dt, and end-diastolic length (EDL) was determined at the onset of left ventricular isovolumetric contraction. Values for five beats of ESL and EDL were averaged, and %SS was calculated by use of the equation $\%SS = [(EDL - ESL)/EDL] \times 100$.

Thirty minutes were allowed to attain stable circulation and to wash out isoflurane after setup of the equipment. Through the injection port, the anesthetics were injected over a 10-s period directly into the circuit that supplied blood to the LCX. First, varying doses of each anesthetic were injected, i.e., etomidate at 0.4, 0.8, 1.6, and 3.2 mg, ketamine or propofol at 0.8, 1.6, 3.2, and 6.4 mg, and fentanyl at 2.5 and 5.0 μg. Second, the effect of combining propofol and fentanyl was examined by adding 0, 2.5, and 5.0 μg of fentanyl to 6.4 mg of propofol. Each agent was diluted to 1 ml with normal saline. The types of anesthetics and the doses were varied randomly in each experiment. Measurements were made 20 s before bolus injection as control values and 30 s after the end of injection when %SS had reached a nadir. Values for all parameters except LVEDP obtained after injections were divided by control values and expressed as percentages.

Data were expressed as means ± SE. Comparisons with control values were performed using the paired Student's *t*-test. Comparisons between groups were performed by analysis of variance and Student's *t*-test for unpaired data with the Bonferroni correction. A $P$ value of less than 0.05 was considered significant.

## Results

The baseline values were as follows: CO, 1.39 ± 0.11 l·min$^{-1}$; LVEDP, 3.38 ± 0.38 mmHg; LVdP/dt, 2366.3 ± 382.8 mmHg·s$^{-1}$; CXF, 24.8 ± 1.8 ml·min$^{-1}$; %SS, 23.2 ± 0.97%. LV dP/dt was not influenced by etomidate, whereas it was decreased by both ketamine and propofol at a dose of 6.4 mg. LVEDP was increased by etomidate at a dose of 3.2 mg, and by ketamine and propofol at a dose of 6.4 mg. MAP, CO, EDL, and CXF were not influenced by these agents (Table 1). Etomidate, ketamine, and propofol significantly reduced %SS in a dose-dependent manner (Fig. 2). Etomidate reduced %SS to 86.9 ± 2.2% and 75.5 ± 1.4% of control at doses of 1.6 and 3.2 mg, respectively. Ketamine reduced %SS to 88.1 ± 1.9% and 76.5 ± 1.1% of control at doses of 3.2 and 6.4 mg, respectively. Propofol reduced %SS to 82.2 ± 1.8% of control at a dose of 6.4 mg.

Fentanyl alone had no effect on myocardial performance at a dose of 2.5 or 5.0 μg. As for the interaction of fentanyl with propofol, fentanyl at a dose of either 2.5 or 5.0 μg did not influence the effect of propofol on %SS, i.e., 6.4 mg propofol reduced %SS to 82.3 ± 3.5% and 83.1 ± 2.7% of control in the absence and presence of 5.0 μg of fentanyl, respectively (Fig. 3).

## Discussion

The present experimental system was suitable for analyzing the direct myocardial effects of anesthetics while avoiding systemic hemodynamic effects on cardiovascular reflexes. The specific features are as follows. (1) The doses of agents injected into the coronary artery were small for the whole body. (2) Heart rate was controlled at 100 bpm by ventricular pacing following creation of an A–V block to avoid the changes in regional contraction that accompany changes in heart rate. (3) Mean arterial pressure was controlled to stabilize myocardial oxygen consumption and to avoid baroreflex. (4) The area exposed to the agents was less than half of the left ventricle, so that changes in %SS can be attributed solely to changes in myocardial contractility. (5) There is a limitation in the present system. The agents at bolus doses of 0.4–6.4 mg were injected over only a 10-s period. The LCX flow was about 25 ml·min$^{-1}$, and thus the concentrations of agents become about 0.1–1.5 mg·ml$^{-1}$,

**Table 1.** Cardiovascular effects of etomidate, ketamine, and propofol

| Variable | | Bolus injection dose (μg) | | | | |
|---|---|---|---|---|---|---|
| | | 400 | 800 | 1600 | 3200 | 6400 |
| MAP (%) | E | 100.3 ± 2.5 | 98.1 ± 2.0 | 98.2 ± 2.4 | 96.4 ± 2.3 | |
| | K | | 98.6 ± 3.0 | 97.7 ± 2.9 | 94.6 ± 3.3 | 95.2 ± 2.6 |
| | P | | 98.8 ± 4.1 | 99.1 ± 4.2 | 95.0 ± 3.1 | 95.1 ± 3.2 |
| CO (%) | E | 99.4 ± 2.0 | 98.8 ± 1.3 | 98.8 ± 1.5 | 95.6 ± 1.9 | |
| | K | | 99.1 ± 1.2 | 99.0 ± 1.8 | 98.0 ± 1.5 | 95.2 ± 2.6 |
| | P | | 98.5 ± 1.0 | 98.5 ± 1.2 | 98.1 ± 0.9 | 92.3 ± 1.2 |
| LVEDP (mmHg) | E | 0.0 ± 0.2 | 0.5 ± 0.2 | 0.5 ± 0.3 | 1.1 ± 0.3* | |
| | K | | 0.0 ± 0.1 | 0.3 ± 0.3 | 0.6 ± 0.3 | 0.8 ± 0.3* |
| | P | | 0.1 ± 0.4 | −0.5 ± 0.3 | −0.8 ± 0.2 | 1.5 ± 0.3* |
| EDL (%) | E | 101.5 ± 3.2 | 101.2 ± 2.8 | 100.8 ± 3.4 | 100.2 ± 3.1 | |
| | K | | 102.1 ± 4.6 | 101.2 ± 4.0 | 100.9 ± 3.6 | 101.3 ± 4.2 |
| | P | | 101.5 ± 3.9 | 101.2 ± 4.0 | 102.1 ± 3.5 | 100.9 ± 3.9 |
| LVdP/dt (%) | E | 98.3 ± 1.2 | 99.5 ± 1.3 | 98.0 ± 1.9 | 93.9 ± 1.2 | |
| | K | | 100.3 ± 1.6 | 100.1 ± 1.5 | 96.8 ± 1.3 | 90.1 ± 2.7* |
| | P | | 98.7 ± 1.5 | 95.3 ± 1.6 | 93.7 ± 1.6 | 87.4 ± 1.8* |
| CXF (%) | E | 100.9 ± 3.3 | 104.3 ± 1.7 | 105.6 ± 2.6 | 110.4 ± 5.0 | |
| | K | | 104.0 ± 2.1 | 100.0 ± 2.7 | 112.1 ± 7.3 | 115.1 ± 5.6 |
| | P | | 92.9 ± 1.5 | 95.2 ± 2.3 | 95.2 ± 4.2 | 90.7 ± 3.8 |
| %SS (%) | E | 100.7 ± 2.4 | 98.9 ± 1.7 | 86.9 ± 6.3* | 75.5 ± 4.0*§ | |
| | K | | 101.3 ± 2.7 | 99.6 ± 2.7 | 88.1 ± 5.3* | 76.5 ± 3.1*# |
| | P | | 100.7 ± 2.2 | 93.6 ± 2.5 | 92.0 ± 4.0 | 82.2 ± 1.8* |

Values are means ± SD; n = 8. E, Etomidate; K, ketamine; P, propofol; MAP, mean arterial pressure; CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; EDL, end-diastolic length; LVdP/dt, left ventricular dP/dt max; CXF, LCX blood flow; %SS, % systolic shortening.
*Significantly ($P < 0.05$) different from control.
§Significantly ($P < 0.05$) different from 3200 μg of ketamine.
#Significantly ($P < 0.05$) different from 1600 μg of etomidate.

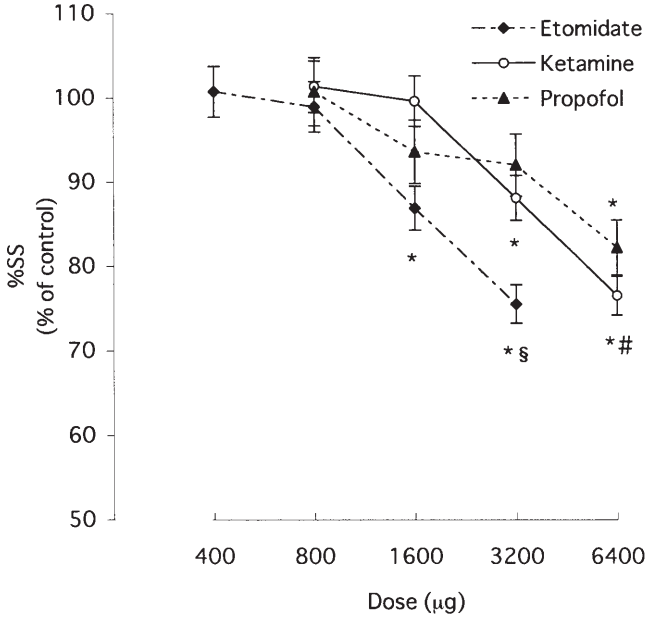


**Fig. 2.** Effects of intracoronary etomidate, ketamine, and propofol on %SS. Values are means ± SE. *$P < 0.05$ compared with control. §$P < 0.05$ compared with 3200 μg of ketamine. #$P < 0.05$ compared with 1600 μg of etomidate

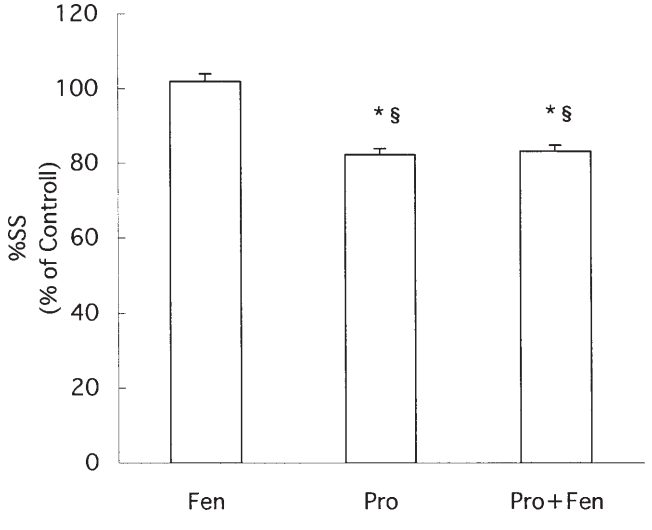


**Fig. 3.** Effects of intracoronary injection of 5 μg of fentanyl (*Fen*), 6400 μg of propofol (*Pro*), and the combination (*Pro* + *Fen*) on %SS. Values are means ± SE. *$P < 0.05$ compared with control. §$P < 0.05$ compared with 5 μg of fentanyl

which seems to deviate from the clinical range. Bolus injections over a 10-s period may not have allowed sufficient time for transfer of agents from the blood to the myocardium. Therefore, the relations between the doses and clinical concentrations are unclear in our study. However, we can compare the direct effects of agents using this system.

The %SS was decreased with 1.6 and 3.2 mg of etomidate (86.9% and 75.5%, respectively), 3.2 and 6.4 mg of ketamine (88.1% and 76.5%, respectively), and 6.4 mg of propofol (82.2%). The %SS values with 1.6 and 3.2 mg of etomidate were similar to those with 3.2 and 6.4 mg of ketamine, respectively, and therefore the myocardial depressant effect of etomidate is about twice as potent as that of ketamine on the basis of injection doses. However, etomidate is 5–10 times more potent than ketamine in anesthetic efficiency ($0.3\,mg\cdot kg^{-1}$ for etomidate and $2\,mg\cdot kg^{-1}$ for ketamine in induction dose). Thus, the depressant effect of ketamine would be more than twice as potent as that of etomidate on the basis of clinical doses. The %SS value of 6.4 mg of propofol was similar to those of 3.2 and 6.4 mg of ketamine. The clinical doses of propofol and ketamine are similar, and thus the myocardial depressant effect of ketamine would be similar to or slightly more than that of propofol on the basis of both injection and clinical doses.

LVEDP was increased and LVdP/dt was decreased with only the highest dose of each agent, whereas CO was not influenced at any dose. These parameters reflect the total function of the left ventricle, which is only partially exposed to the agents because of the injection into the LCX. Thus, they are less sensitive than %SS in terms of contractile depression.

The induction of general anesthesia with ketamine would produce cardiovascular stimulation through its sympathomimetic effects. However, in the presence of an impaired sympathetic nervous system, ketamine would produce a direct myocardial depressant effect. Some in vitro studies demonstrated that ketamine had a direct myocardial depressant effect [8,9]. The concentration of ketamine at which isometric contractions were reduced by 50% (IC50) ranged about 20 to $80\,\mu g\cdot ml^{-1}$. Although the concentration of ketamine 5 min after induction was reported as 60 μM (about $16\,\mu g\cdot ml^{-1}$) [10], a greater plasma concentration can be expected immediately after induction. For comparison of the concentrations in vitro with clinical concentrations, protein binding of agents must be considered, because only free agents are active. The fraction of ketamine bound to plasma proteins is only 20%. Therefore, ketamine seems to have a myocardial depressant effect in a clinical range of concentrations.

The induction of general anesthesia with etomidate was reported to produce minimal cardiovascular depression [5]. The IC50 of etomidate was reported to be about $10\,\mu g\cdot ml^{-1}$ in isolated ferret ventricular myocardium [11] and $40\,\mu g\cdot ml^{-1}$ in blood-perfused dog papillary muscle [12]. Because etomidate is about 77% bound to plasma proteins, the free concentrations of etomidate in these two studies are similar. The concentration of etomidate 4 min after induction was reported as about $0.3\,\mu g\cdot ml^{-1}$[13]; the free concentration will not exceed $1\,\mu g\cdot ml^{-1}$ even immediately after induction. Therefore, it was concluded that etomidate had a myocardial depressant effect only at supraclinical concentrations in both in vivo and in vitro studies.

In contrast, whether propofol depresses myocardial contractility is still controversial, despite extensive studies. Most in vitro studies found that propofol had direct myocardial depressant effects only at supraclinical concentrations [14,15]. The IC50 of propofol in these studies ranged from about 90 to 300 μM ($16–50\,\mu g\cdot ml^{-1}$). The clinical concentration of propofol was reported to range less than $10\,\mu g\cdot ml^{-1}$ [16], and propofol becomes about 98% bound to plasma proteins. The calculated free concentration should range less than $0.2\,\mu g\cdot ml^{-1}$, and therefore the IC50 of propofol would be far from the clinical range. However, some investigators studied the direct effect of propofol on myocardial contractility in vivo and demonstrated myocardial depressant effects at clinically relevant concentrations using various indices relatively independent of changes in preload and afterload: the end-systolic pressure-length relationship [17] and the regional preload recruitable stroke-work relationship [18]. Ismail et al. [7] carried out intracoronary continuous infusions in a canine model similar to one used in our study. Propofol caused cardiac depression only at an infusion rate of $300\,\mu g\cdot ml^{-1}$: the calculated blood concentration was $15\,\mu g\cdot ml^{-1}$, which was not as much as the clinical concentration.

Stowe et al. [19] in isolated guinea pig hearts and more recently Gelissen et al. [20] in isolated human atrial muscle carried out comparative studies of the direct myocardial depressant effects of multiple intravenous anesthetics. Stowe reported the IC50 (μM) as follows: ketamine, 323 ± 7; etomidate, 82 ± 2; and propofol, 91 ± 4. Gelissen reported values as follows: ketamine, 303 ± 54.3; etomidate, 133 ± 12.7; and propofol, 235 ± 47.8. In their studies, the IC50 values ($\mu g\cdot ml^{-1}$) of ketamine, etomidate, and propofol were 83–88, 20–32, and 16–42, respectively. When these values are applied to the whole body taking into account protein binding, the IC50 ($\mu g\cdot ml^{-1}$) of ketamine, etomidate, and propofol become about 104–110, 87–140, and 800–2000, respectively. Therefore the depressant effect of etomidate seems comparable to that of ketamine, and the depressant effect of propofol seems to be 1/8–1/20 of that of ketamine.

The reason for the difference in the results between the in vitro studies and the present study might be as follows. Although the time course of protein binding is unknown, these agents would not be equilibrated for protein binding immediately after bolus injections. Therefore, the fraction of unbound agents would remain higher than that estimated for the static condition, and these agents may depress myocardial contractility at lower blood concentrations than the concentrations calculated from in vitro data and the fraction of protein binding. The protein binding of propofol is especially high, and thus it is possible that the unbound fraction of propofol might remain at a high enough concentration to exert physiological effects.

In the present study, the volume of the extracorporeal circuit between the injection port and the LCX was 7 ml, and the LCX flow was about 25 $ml \cdot min^{-1}$. Thus, it took about 17 s to reach the LCX after injection. The arm-to-tongue circulation time is about 15 s in humans, and therefore intracoronary administration of agents was allowed a comparable time for equilibration after peripheral intravenous administration.

Although fentanyl alone was reported to produce minimal changes in hemodynamic values [2], it was shown that the combination of propofol with fentanyl resulted in further decrease in arterial blood pressure and cardiac output as compared with propofol alone [3]. These hemodynamic changes were reported to be due to fentanyl-induced decrease in heart rate and SVR, but the interaction of propofol and fentanyl on myocardial contractility is unclear. In our study, fentanyl had no effect on myocardial performance and did not enhance the direct myocardial depressant effect of propofol. Therefore, the enhanced hypotension with a combination of propofol and fentanyl would not be due to the enhanced myocardial depressant effect.

In conclusion, on the basis of clinical doses, the direct myocardial depressant effect of ketamine is more than twice as potent as that of etomidate and slightly more than that of propofol. Fentanyl has no inotropic effect and does not enhance the direct myocardial depressant effect of propofol.

## References


1. Claeys MA, Gepts E, Camu G (1988) Haemodynamic changes during anesthesia induced and maintained with propofol. Br J Anesth 60:3–9
2. Tamminato T, Takki S, Toikka P (1970) A comparison of the circulatory effects in man of the analgesics fentanyl, pentazocine and pethidine. Br J Anesth 42:317–324
3. Van Aken H, Meinshausen E, Prien T, Brussel T, Heinecke A, Lawin P (1998) The influence of fentanyl and tracheal intubation on the hemodynamic effects of anesthesia induction with propofol/$N_2O$ in humans. Anesthesiology 68:157–163
4. Tweed WA, Minuck M, Mymin D (1972) Circulatory responses to ketamine anesthesia. Anesthesiology 37:613–619
5. Criado A, Maseda J, Naverro E, Escarpa A, Avello F (1980) Induction of anesthesia with etomidate: haemodynamic study of 36 patients. Br J Anesth 52:803–806
6. Buffington CW (1989) The magnitude and duration of direct myocardial depression following intracoronary local anesthetics: a comparison of lidocaine and bupivacaine. Anesthesiology 70:280–287
7. Ismail EF, Kim S-J, Salem MR, Crystal GJ (1992) Direct effects of propofol on myocardial contractility in situ canine hearts. Anesthesiology 77:964–972
8. Endou M, Hattori Y, Nakaya H, Gotoh Y, Kanno M (1992) Electrophysiologic mechanism responsible for inotropic responses to ketamine in guinea pig and rat myocardium. Anesthesiology 76:409–418
9. Rusy BF, Amuzu JK, Bosscher HA, Redon D, Komai H (1990) Negative inotropic effect of ketamine in rabbit ventricular muscle. Anesth Analg 71:275–278
10. Idvall J, Ahlgren I, Aronsen KF, Stenberg P (1979) Ketamine infusions: pharmacokinetics and clinical effects. Br J Anesth 51:1167–1172
11. Mattheussen M, Housmans PR (1993) Mechanism of the direct, negative inotropic effect of etomidate in isolated ferret ventricular myocardium. Anesthesiology 79:1284–1295
12. Kissin I, Motomura S, Aultman DF, Reves JG (1983) Inotropic and anesthetic potencies of etomidate and thiopental in dogs. Anesth Analg 62:961–965
13. Van Hamme MJ, Ghoneim MM, Ambre JJ (1978) Pharmacokinetics of etomidate, a new intravenous anesthetic. Anesthesiology 49:274–277
14. Cook DJ, Housmans PR (1994) Mechanism of the negative inotropic effect of propofol in isolated ferret ventricular myocardium. Anesthesiology 80:859–871
15. Azari DM, Cork RC (1993) Comparative myocardial depressive effects of propofol and thiopental. Anesth Analg 77:324–329
16. White PF (1988) Propofol: pharmacokinetics and pharmacodynamics. Semin Anesth 7:4–20
17. Coetzee A, Fourie P, Coetzee J, Badenhorst E, Rebel A, Bolliger C, Uebel R, Wium C, Lombard C (1989) Effect of various propofol plasma concentrations on regional myocardial contractility and left ventricular afterload. Anesth Analg 69:473–483
18. Pagel PS, Warltier DC (1993) Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. Anesthesiology 78:100–108
19. Stowe DF, Bosnjak ZJ, Kampine JP (1992) Comparison of etomidate, ketamine midazolam, propofol, and thiopental on function and metabolism of isolated hearts. Anesth Analg 74:547–558
20. Gelissen HPMM, Epema AH, Henning RH, Krijnen HJ, Hennis PJ, Hertog A (1996) Inotropic effect of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle. Anesthesiology 84:397–403