The Seoul Journal of Medicine
Vol. 33, No. 2: 153-160, June 1992

Direct Effects of Propofol on the Left Ventricular Papillary Muscles of Rats Compared with Other Intravenous Induction Agents

Sang Chul Lee and Young Zin Sohn *

Department of Anesthesiology, Seoul National University, College of Medicine, Seoul 110-744, Korea, and
Department of Anesthesiology, School of Medicine UCLA, Los Angeles, CA 90024, U.S.A.*

= Abstract =**The isometric contractions of isolated rat myocardiums to propofol were compared with those to thiopental, etomidate, and brevital. 40 rat left ventricular papillary muscles were evenly divided into four groups and were exposed to the mean maximum post-induction plasma concentration and its double concentration in random order. Both concentrations of propofol showed 17.5% to 22.5% depression in Tpd, $+dp/dt_{max}$, and $-dp/dt_{max}$, which was the greatest among four agents, while thiopental revealed the least depression. Brevital and etomidate depressed three parameters to a similar degree. In Tr, TPT, and $RT_{90\%}$, there were only negligible changes in all four drugs in both concentrations.**

We might say that the depression of myocardial contractility by propofol is, in part, a important cause of hypotension. Therefore propofol should be used with caution in patients with a depressed myocardial contractility.

Key Words: *Isometric contraction, Propofol, Thiopental, Etomidate, Brevital*

INTRODUCTION

Propofol(2,6 diisopropylphenol) is a new intravenous induction agent that is currently undergoing clinical trials in the world, including Korea. It commonly causes systemic arterial hypotension which is dose related (Cummings *et al.* 1984; Glen and Hunter 1984; Kay *et al.* 1984; Nightingale *et al.* 1985; Grounds *et al.* 1985; Fahmy *et al.* 1985; Claeys *et al.* 1988; Coates *et al.* 1987, Monk *et al.* 1987; Patrick *et al.* 1985; Coates *et al.* 1985), and this effect is lessened when the drug is administered slowly (Fahy *et al.* 1985). Propofol appears to cause more hypotension than equivalent doses of thiopental, etomidate, brevital and thiamylal sodium (Fahy *et al.* 1985; McCollum and Dundee 1986; Henriksson *et al.* 1987; Kaplan *et al.* 1988; Brssel *et al.* 1989, Mackenzie and Grant 1985).

Whether this effect is the result of a decrease in preload, a decrease in afterload, a negative inotropic property of the drug, or the combination of all the above cannot be ascertained from the literature as the results of different studies are conflicting.

The aim of this study was to determine the role, if any, of the direct negative inotropic effect of propofol in causing arterial hypotension.

Received March 1992, and in final form May 1992.
서울대학교 의과대학 마취과학교실 : 이상철
미국 UCLA 의과대학 마취과학교실 : 손영진

The responses of rat myocardiums to propofol were compared to those produced by thiopental, etomidate, and brevital. We used the concentrations we could get from the plasma when these drugs are administered in doses recommended for the induction of anesthesia (low concentration), and the in double concentrations (high concentration).

MATERIALS AND METHODS

Isolated columns of papillary muscle were prepared from left ventricles of rats. The rats were 2-3 months old. Each preparation was placed in an oxygenated (oxygen 95%, carbon dioxide 5%) 80 ml capacity muscle bath containing modified Krebs-bicarbonate solution. The temperature of the bath solution was held constant at 35°C by a thermoregulator (Precision Scientific Co.), and the pH was stabilized at 7.40. One end of the muscle was fixed, and the other was connected to a force displacement transducer (Grass FT03C) and its output recorded on one channel, while another output was connected to the differentiator (Optic Electronics Inc., model 9009) and recorded on another channel of the recorder (Gould Brush Recorder 2400). Each muscle was stimulated (Grass SD0 Stimulator) with 2x8 mm platinum plate electrodes, placed about 10 mm apart parallel to the muscle, at a frequency of 0.25 Hz with a square wave pulse of 6.0 ms duration and voltages 10% above threshold. The length-tension curve of each preparation was determined after 30 minutes of isometric contractions.

Changes in muscle length measured with a micrometer transformer could be detected to 01 mm. The maximum muscle length-tension (the length at the peak of the length-tension curve was 5.41 ± 1.49 mm. The muscle was held at the peak of the length-tension curve for 30 minutes for stabilization, then, peak developed tension (Tpd), resting tension (Tr), maximum rate of tension development ($+dp/dt_{max}$) and relaxation ($-dp/dt_{max}$), time to peak tension (TPT), and relaxation time ($RT_{90\%}$, time for Tpd to decay 90% of maximum) were recorded at a paper speed of 100 mm per second.

At the maximum muscle length of the length-tension curve of each preparation, 40 muscles were evenly divided into 4 groups, and each group was exposed to 2 different concentrations of one intravenous induction agent in random order. After testing one concentration, the second concentration was tried after a wash-out with the same physiologic solution and 30 minutes' stabilization. The concentrations used were: the propofol group to 2.5 μg/ml and 5.0 μg/ml of propofol, the thiopental group to 5.0 μg/ml and 10.0 μg/ml of thiopental, the brevital group to 1.5 μg/ml and 3.0 μg/ml of brevital, and the etomidate group to 0.3 μg/ml and 0.6 μg/ml of etomidate. All of the concentrations we used were the plasma concentrations we could get when we administered the recommended clinically equipotent doses and their double doses.

The percent changes from the control values of each parameter in each group were obtained. Data for the groups and their concentrations were compared with multiple comparison with a Duncun test after analysis of variances. We accepted the value of $p<0.05$ as statistically significant.

RESULTS

Fig. 1 shows a typical tracing for the effects of a low concentration of intravenous induction agents on Tpd in isometric contraction. Propofol showed greatest depression among the four drugs, while thiopental revealed the least depression. Brevital and etomidate depressed the peak developed tension to a similar degree. This tendency could be easily identified in Table 1. Both concentrations of propofol showed about 17.5 to 22.5% depression in Tpd, $+dp/dt_{max}$, and $-dp/dt_{max}$ and thiopental showed the least depression which was less than 3% even in high concentration. Brevital and etomidate showed a peculiar phenomenon, which was the appearance of a greater depression in low concentration than in high

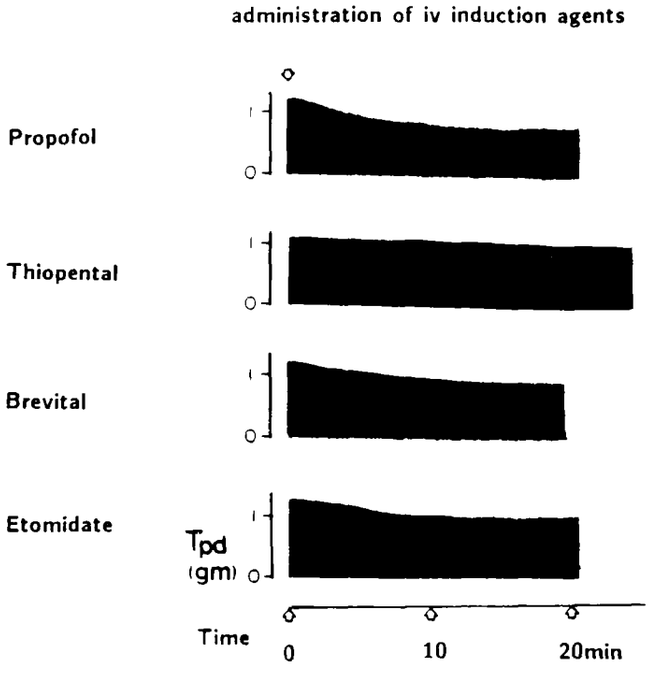

Fig. 1 Typical tracing of the effects by the low concentration of propofol, thiopental, brevital and etomidate in peak developed tension.

concentration. They depressed Tpd, $+dp/dt_{max}$, and $-dp/dt_{max}$ about 8.0 to 11.5% in low concentration but only 1.5 to 6.0% in high concentration, which was statistically significant only in brevital when we compared low with high concentration(Fig. 2, 4, 5). Etomidate showed a significant difference in $-dp/dt_{max}$ only (Fig. 5). The difference between propofol and the other three drugs was statistically significant in both concentrations and also the difference between thiopental and the other two drugs (brevital and etomidate) was statistically significant in low concentration.

In Tr, TPT, and $RT_{90\%}$, there were only negligible changes with all four drugs in both concentrations. Only brevital showed a significant difference from thiopental in TPT in low concentration (Table 1, Figs. 3, 6, 7).

DISCUSSION

Propofol (Diprivan) is a substituted phenol that is being studied as a new intravenous anesthetic induction agent. The drug was originally formulated in cremephor EI, which caused a high incidence of anaphylactoid reactions. Subsequently, it has been produced as a 1% aqueous emulsion with 10% soybean oil, 1.2% egg phosphatide, and 2.5% glycerol (Mackenzie and Grant 1985; Grounds *et al.* 1985) in order to avoid the severe hemodynamic responses seen with use of the old formulation. Later studies in animals and man have shown propofol to be safe and effective for mainten-

Table 1. Effects of Propofol, Thiopental, Brevital and Etomidate on Isometric Contractions of Isolated Left Ventricular Papillary Muscles of Rats

		Tpd	Tr	$+dp/dt_{max}$	$-dp/dt_{max}$	TPT	$RT_{90\%}$
Propofol	L	−19.61±6.19	−1.61±3.69	−17.65± 5.43	−17.90±6.60	−4.32±5.72	−1.20±4.91
	H	−22.31±7.43	0.16±6.12	−21.79± 5.86	−20.40±5.15	−0.73±6.77	−0.68±5.31
Thiopental	L	− 0.08±8.02*	1.79±5.20	− 0.14± 7.44*	− 1.00±7.17*	1.08±6.09	0.11±3.52
	H	− 2.99±9.91*	1.96±5.88	− 0.70±11.61*	− 3.09±13.18*	−0.89±4.36	1.94±3.96
Brevital	L	− 9.19±5.56*#	0.22±2.88	− 8.08± 4.23*#	− 7.97±4.41*#	0.59±4.08*	−0.05±5.69
	H	− 1.75±2.30*	0.30±3.29	− 3.44± 4.45*	− 2.90±5.04*	0.71±2.26	1.29±3.50
Etomidate	L	− 8.78±6.35*#	1.53±5.42	− 9.50± 6.02*#	−11.39±7.80#	0.55±5.01	1.26±7.73
	H	− 5.76±8.64*	0.43±4.43	− 5.51± 8.40*	− 3.53±6.53*	−2.32±5.42	−0.10±3.95

Data are mean±S.D. of Per Cent Changes from Control

L : low concentration, 2.5, 5.0, 1.5, and 0.3 μg/ml for propofol, thiopental, brevital and etomidate, respectively

H : high concentration, 5.0, 10.0, 3.0, and 0.6 μg/ml for each drug, respectively

*, #, @ : $p<0.05$ comparing with propofol, thiopental and Brevital, respectively

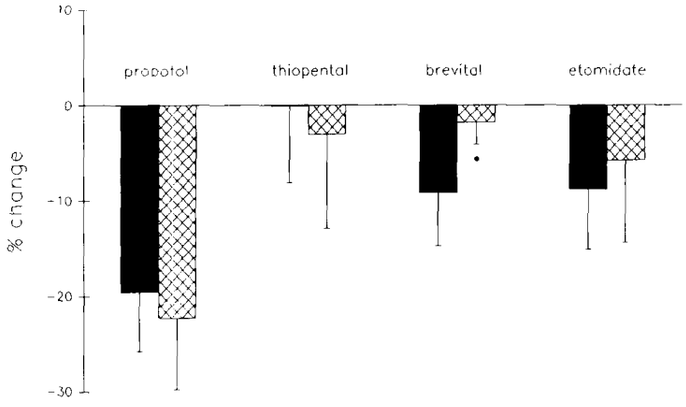

Fig. 2. Percent change from control in peak developed tension. filled box: low concentration, crosshatch: high concetration
* $p<0.05$ comparing with low concentration

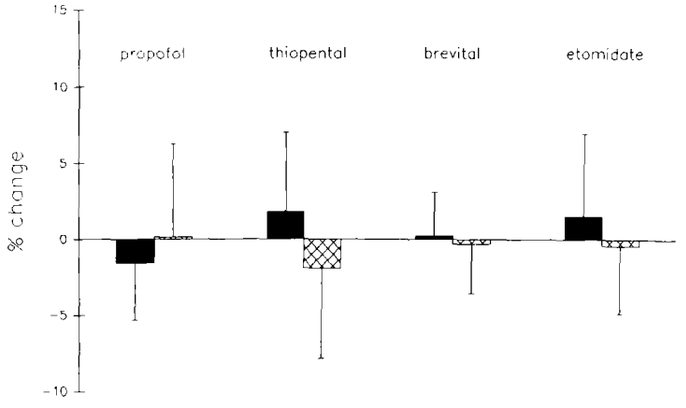

Fig. 3. Percent change from control in resting tension. filled box: low concentration, crosshatch: high concetration
* $p<0.05$ comparing with low concentration

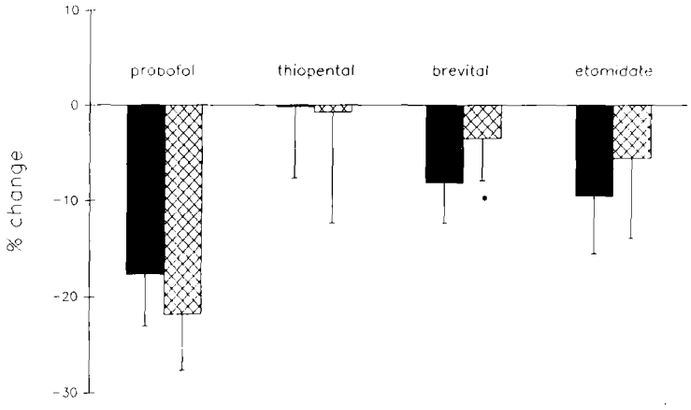

Fig. 4. Percent change from control in maximum rate of tension. * $p<0.05$ comparing with low concentration filled box: low concentration, crosshatch: high concetration

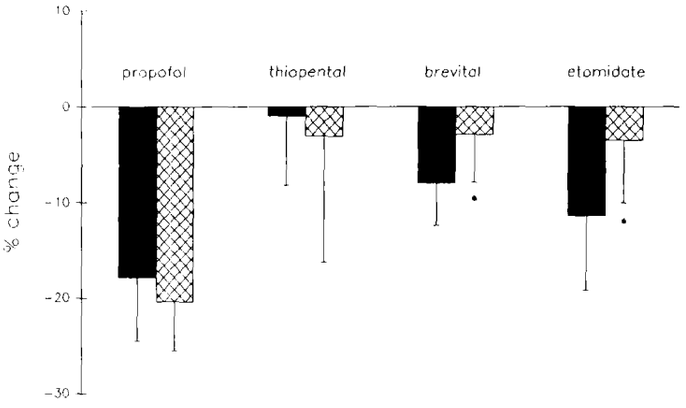

Fig. 5. Percent change from control in maximum rate of tension relaxation. * $p<0.05$ comparing with low concentration filled box: low concentration, crosshatch: high concetration

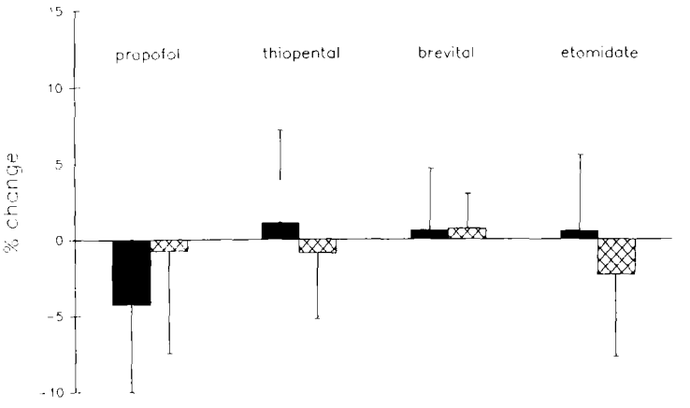

Fig. 6. Percent change from control in time to peak tension. filled box: low concentration, crosshatch: high concetration
* $p<0.05$ comparing with low concentration

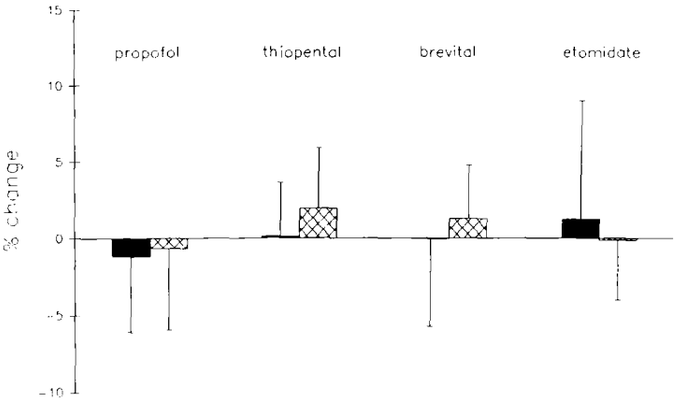

Fig. 7. Percent change from control in time for tension to decay 90% of maximum. * $p<0.05$ comparing with low concentration filled box: low concentration, crosshatch: high concetration

ance when used in incremental doses during short procedures (Kay *et al.* 1984; Fahy *et al.* 1985, Hunter *et al.* 1985; Yongberg *et al.* 1987) by virtue of its short duration of action and rapid elimination phase (Adam *et al.* 1983). However, the data from healthy patients demonstrated significant decreases in mean arterial pressure even though the mechanism is still not clear (Yongberg *et al.* 1987).

Hemodynamic changes after induction of anesthesia are the result of both direct and indirect effects on the myocardium and peripheral blood vessels. The indirect effects are mediated by changes in peripheral receptors and central control mechanisms. Under normal circumstances, it may be difficult to isolate the contribution that individual mechanisms make to the overall hemodynamic response to a drug. Cardiopulmonary bypass has been shown to be a useful model for studying the isolated effects of anesthetic drugs on peripheral vascular resistance. But it is better to isolate the myocardium to understand the direct effect of any anesthetic agent on myocardial contractility like in our experimental model.

In vitro experiment is very rare for propofol. As far as we know, this study is the first one which measured the depression of isometric contraction in isolated myocardial muscle with propofol. A lot of in vivo studies were done by many investigators for propofol, but there was a pitfall for interpretating the results of their studies. They usually used other anesthetic agents for their studies, therefore they could not exclude that other agents, such as anesthetics, modified the hemodynamic or cardiodynamic alterations associated with propofol. Thus we used the isolated papillary muscle model for the evaluation of the direct and unique effect of propofol on myocardium without using other drugs.

Comparisons of intravenous anesthetic agents require the use of equipotent doses. A study comparing the effects of different doses of propofol, thiopental, etomidate and brevital does not exist. Grounds *et al.* (1986) and Kissin *et al.* (1983) reported that the recommended doses for induction of anesthesia in humans for etomidate, thiopental and propofol were 0.3 mg/kg, 4.0 mg/kg, and 2.5 mg/kg. But Mackenzie and Grant(1985) used propofol 2.5 mg/kg, brevital 1.5 mg/kg, and thiopental 5 mg/kg for induction of anesthesia. We used 5 mg/kg of thiopental because our clinical experiences indicated that 5 mg/kg of thiopental is usually adequate for the induction of anesthesia. We evaluated the direct effects of the mean maximum concentrations we could get after administration of these induction doses. We also observed the effects of double doses because we sometimes administer greater amounts of these agents to patients due to various clinical conditions or by an inadvertent injection.

Propofol brings more hypotension than equivalent doses of thiopental, brevital and etomidate (Fahy *et al.* 1985; Henriksson *et al.* 1986; Kaplan *et al.* 1988; Brssel *et al.* 1989; Mackenzie and Grant 1985). This may be related to the greater decrease in peripheral vascular resistance caused by propofol (Lippmann *et al.* 1986). Boer *et al.* (1990) reported that the decrease in peripheral vascular resistance was comparable to the decrease in arterial pressure, suggesting that vasodilatation may be a major factor in propofol-induced hypotension. They also suggested that other contributing factors may be a lesser increase in heart rate in response to hypotension and impairment of myocardial contractility. Propofol causes resetting of the baroreceptor reflex control of heart rate without depression of baroreflex sensitivity (Cullen *et al.* 1987). This allows low heart rates to be sustained despite a decrease in arterial pressure. But in our study, propofol brought about 20% decreases of Tpd, $+dp/dt_{max}$, and $-dp/dt_{max}$, which occupied the main proportion of the decrease in arterial pressure. We eliminated the possible interaction of systemic vascular vasodilation, changes in heart rate and baroreflex activity, on the mechanism of hypotension, thus, we might say that the one of the important mechanisms for hypotension induced by propofol could be, in part, the de-

pression of myocardial contractility.

Drugs suitable for use in healthy patients frequently have different or more significant effects in patients with cardiac disease. Langley and Heel (1988) reported that in both patients without cardiac disease and in those with severe coronary artery disease, propofol causes about a 20% decrease in cardiac index (Patrick *et al.* 1985; Lepage *et al.* 1988) which is similar to that caused by thiopental. This observation is compatible with our result for propofol but not for thiopental. Our results suggested that the mechanism of hypotension brought by thiopental is different from propofol. Lippmann *et al.* (1986) reported that the decreases in left-sided heart parameters are much greater with propofol than with thiopental. Therefore, we might say that the hypotension caused by thiopental is mainly due to the effect on peripheral resistance rather than on myocardial contractility.

The responses in contractility to brevital and etomidate were not dose related. They showed a lesser degree of depression in Tpd, $+dp/dt_{max}$ and $-dp/dt_{max}$ than propofol. Even though they did not show the severe hemodynamic changes, the systemic hypotension which could be brought by etomidate and brevital might be, at least partly, the result of the depression in myocardial contractility. We could not explain why, in high concentration, brevital and etomidate revealed lesser depression than in low concentration. There is a possibility that brevital and etomidate lose their depressive activity on myocardium when we administer a high dose because of a change in a certain component or the conditions in the muscle bath, which we have to investigate in a future study. Another possible explanation for this phenomenon is that it might be the result of the insufficient duration between the two concentrations. Some investigators recommended a 60 minutes' waiting time for this kind of experimental model but some thought 30 minutes was enough. We administered the second concentration of each drug after a washout and 30 minutes' stabilization period. The short waiting time and the low temperature of the physiologic solution could have delayed the recovery time especially for brevital and etomidate. Possibly a low concentration could have been injected into the muscle bath more frequently after high concentration by chance because we performed the experiment in random order by the double blind method to eliminate any preoccupation.

There was no protein at all in the muscle bath, the unbound fractions of propofol, thiopental, brevital and etomidate acutely increased and the effect on myocardial contractility could be strengthened. This might be partly a reason why some of our results are different from other studies done on aminals and man. For example, propofol is a weak organic acid that is bound extensively to plasma albumin, with a free fraction of only 2-3% (Russell *et al.* 1989).

Williams *et al.* (1988) observed that there is evidence that propofol does not alter left ventricular performance in patients with coronary artery disease and good left ventricular function. However other studies in cardiac surgical patients suggest that the drug may cause some myocardial depression in addition to vasodilatation (Patrick *et al.* 1985). This may be secondary to a reduction in coronary artery blood flow consequent upon hypotension (Kaplan *et al.* 1988). The reason why propofol causes arterial hypotension is still obscure and needs clarification because there are a lot of conflicting observations.

Lepage *et al.* (1988) observed the reduction in myocardial contractility but, at the same time, oxygen extraction ratio decreased with the difference between arterial and mixed venous oxygen contents by propofol. He suggested that propofol decreased the oxygen demand which contributed to the decrease in cardiac index and made the circulation efficient, even in coronary artery disease patients, if blood pressure did not fall by a severe degree. We did not observe any oxygen utilization and metabolic components in this study but these factors should be taken into consideration if we want to elucidate the mechanism

and the risk of hypotension with propofol.

Tr, TPT, and $RT_{90\%}$ showed no remarkable change after administration of the four different intravenous induction agents, except that brevital showed a statistically signicant difference to thiopental at low concentration in TPT. Propofol showed a 4.32% decrease of TPT at low concentration, which was the greatest depression among the four drugs. This finding again was evidence that propofol is the strongest myocardial depressant. But at high concentration, propofol showed only a 0.73 % depression in TPT, which might be due to the bias in reading the figures drawn by the physiograph. Because the change of the baseline is very delicate and is disturbed easily with any electrical interference, and we read the results only with our naked eyes, misinterpretations can occur sometimes especially for changes in, such as TPT, Tr and $RT_{90\%}$. The reason why we did this study by double blind method was merely due to this difficulty in reading the results, because the change of the baseline was so critical for these three parameters. Thiopental, brevital and etomidate did not bring a prolongation of the time for peak tension and relaxation time. And all four intravenous induction agents did not change the resting tension, which meant that they didn't make the myocardium more rigid than before the muscle was exposed to the drugs.

In summary, propofol revealed the greatest depression of isometric contraction and thiopental, the least. We might suggest that the cause of hypotension with thiopental is mainly due to vasodilation, while with propofol the depression of myocardial contractility might be important. Brevital and etomidate stayed in between thiopental and propofol. Our findings indicate that propofol should be used with caution in patients with limited cardiovascular reserve, especially in those whose myocardial contractility is already depressed.

REFERENCES

Adam HK, Briggs LP, Bahar M, douglas EJ, Dundee JW. Pharmacokinetic evaluation of ICI 35868 in man. Br J Anaesth 1983; 55:97-102

Boer F, Ros P, Bobill JG, Brummelen P, Krogt J. Effect of propofol on peripheral vascular resistance during cardiopulmonary bypass. Br J Anaesth 1990; 65:184-9

Brssel T, Theissen JL, Vigfusson G, Lunkenheimer PP, Aken HV, Lawin P. Hemodynamic and cardiodynamic effects of propofol and etomidate: Negative inotropic properties of propofol. Anesth Analg 1989; 69:35-40

Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988; 60:3-9

Coates DP, Monk CR, Prys-Roberts C, Turtle M, Spelina KR, Norley I. Hemodynamic effects of the infusion of the emulsion of propofol during nitrous oxide anesthesia in humans. Anesth Analg 1987; 66:64-70

Coates DP, Prys-Roberts C, Spelina KR, Monk CR, Norley I. Propofol by intravenous infusion with nitrous oxide: dose requirements and haemodynamic effects. Postgrad Med J 1985; 61:76-9

Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effects of propofol anesthesia on baroreflex activity in humans. Anesth Analg 1987; 66:1115-20

Cummings GC, Dixon J, Kay NH, Windsor JPW, Major E, Morgan M, Sear JW, Spence AA, Stephenson DK. Dose requirements of ICI 35868, a new formulation for induction of anaesthesia. Anaesthesia 1984; 39:1168-71

Fahmy NR, Alkhouli HM, Sunder N, Smith D, Kelly MM. Diprivan: A new intravenous induction agent. A comparison with thiopental. Anesthesiology 1985; 63:A363

Fahy LT, van Mourik GA, Utting JE. A comparison of the induction characteristics of thiopentone and propofol. Anaesthesia 1985; 40:939-44

Glen JB, Hunter SC. Pharmacology of an emulsion formulation of ICI 35868. Br J Anaesth 1984; 56:617-26

Grounds RM, Moore M, Morgan M. The relative

potencies of thiopentone and propofol. Eur J Anaesthesiol 1986; 3:11-7

Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. Anaesthesia 1985; 40:735-40

Henriksson BA, Carlsson P, Hallen B, Hagerdaz M, Lundberg D, Ponten J. Propofol vs thiopentone as anaesthetic agents for short operative procedures. Acta Anaesthesiol Scand 1987; 31:63-6

Hunter SJ, Spencer I McLaren CAB. Propofol induction and maintenance of anaesthesia. Postgrad Med J 1985; 61:101

Kaplan JA, Guffin AV, Mikula S, Dolman J, Profeta J. Comparative hemodynamic effects of propofol and thiamylal sodium during anesthetic induction for myocardial revascularization. J Cardiothoracic Anesth 1988; 2:297-302

Kay NH, Uppington J, Sear JW, Allen MC. Use of an emulsion of ICI 35868 for the induction and maintenance of anaesthesia. Br J Anaesth 1984; 57:736-42

Kissin I, Motomura S, Aultman DF, Reves JG. Inotropic and anesthetic potencies of etomidate and thiopental in dogs. Anesth Analg 1983; 62:961-65

Langley MS, Heel RC. Propofol. A review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anaesthetic. Drugs 1988; 35:334-72

Lepage JYM, Pinaud ML, Helias JH, Juge CM, Cozian AY, Farinotti R, Souron RI. Left ventricular function during propofol and fentanyl anesthesia in patients with coronary artery disease: Assessment with a radionuclide approach. Ansth Analg 1988; 67:949-55

Lippmann M, Pacius R, Gingerich S, Owens R, Mok MS, Charney J, Lee TS, Harley D, Verespej J, Appel P. A controlled study of the hemodynamic effects of propofol vs thiopental during anesthesia induction. Anesth Analg 1986; 65:S89

Mackenzie N, Grant IS. Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anesthesia in day cases. Br J Anaesth 1985; 57:725-31

McCollum JSC, Dundee JW, Comparison of induction characteristics of four intravenous anaesthetic agents. Anaesthesia 1986; 41: 995-1000

Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina KR. Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous oxide anaesthesia. Studies in association with peripheral arterial surgery. Br J Anaesth 1987; 59:954-60

Nightingale P, Healy TEJ, Hargreaves J, McGuiness K, Kay B. Propofol in emulsion formulation. Induction characteristics and venous sequelae. Eur J Anaesthesiol 1985; 2:361-8

Patrick MR, Blair IJ, Feneck RO, Sebel PS. A comparison of the haemodynamic effects of propofol and thiopentone in patients with coronary artery disease. Postgrad Med J 1985; 61:23-7

Russell GN, Wright EL, Fox MA, Douglas EJ, Cockshott ID. Propofol-fentanyl anaesthesia for coronary artery surgery and cardiopulmonary bypass. Anaesthesia 1989; 44:205-8

Williams JP, McArthur JD, Walker WE, Rietsema K, Teunissen E, Bonnenkamp H, Goderie P, Stanley TH. A comparison of the hemodynamics of Diprivan, thiopental, and etomidate for induction of anesthesia in patients with coronary artery disease. Seminars in Anesth 1988; 7:112-5

Yongberg JA, Texidor MS, Smith DI. A comparison of induction and maintenance of anesthesia with propofol to induction with thiopental and maintenance with isoflurane. Anesth Analg 1987; 66:S191