

## The Safety and Efficacy of Esmolol during Myocardial Revascularization

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The safety and efficacy of esmolol during high-dose fentanyl anesthesia were studied in 37 patients undergoing coronary artery bypass grafting (CABG). The anesthetic management consisted of fentanyl 75  $\mu\text{g}/\text{kg}$ , pancuronium 0.15 mg/kg, and  $\text{O}_2$ . To assess the safety of esmolol, it was administered in a double-blind manner to 17 anesthetized patients prior to surgical incision. Infusion of the drug was increased in stepwise fashion to obtain administration rates between 100 and 300  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Esmolol produced small but significant increases in pulmonary capillary wedge pressure (PCWP) ( $8.3 \pm 1.7$  to  $13.2 \pm 2.0$  mmHg) when compared with placebo ( $10.9 \pm 1.0$  to  $12.1 \pm 0.6$  mmHg) ( $P < 0.05$ ). For the other studied parameters (heart rate, mean arterial pressure, central venous pressure, cardiac index, stroke index, left ventricular stroke work index, systemic vascular resistance, and peripheral vascular resistance), no significant differences were observed between esmolol and placebo. To evaluate the efficacy of esmolol, 20 patients were randomly assigned to an esmolol group ( $n = 11$ ) or a placebo group ( $n = 9$ ). The study medication was infused from 5 min before induction through initiation of cardiopulmonary bypass. Infusion of esmolol at 200  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  prevented tachycardia in response to intubation. In the esmolol group the heart rate increased from  $63.4 \pm 2.7$  to  $67.6 \pm 2.9$  beats/min after intubation, while in the placebo group it increased from  $61.4 \pm 4.3$  to  $72.4 \pm 3.4$  beats/min ( $P < 0.05$ ). Furthermore, the increases in mean pulmonary artery pressure and PCWP observed in unstimulated, anesthetized patients were absent during surgical stimulation. Thus, in CABG patients anesthetized with fentanyl, esmolol appears safe and effective in preventing increases in heart rate during stimulation. (Key words: Heart: esmolol; hemodynamics. Neuromuscular blocking drugs: pancuronium. Surgery: cardiac. Sympathetic nervous system, sympatholytic agents: esmolol.)

PATIENTS WITH ISCHEMIC heart disease who are undergoing coronary artery bypass grafting (CABG) are at risk of developing ischemia at any time during the perioperative period. Slogoff *et al.* have observed that the incidence of ischemia during CABG was significantly higher in patients who had hemodynamic abnormalities such as tachycardia ( $>100$  beats/min) before and during anes-

thesia.<sup>1</sup> They also found that intraoperative ischemia was associated with a higher rate of perioperative myocardial infarction. In addition, Thomson *et al.* have shown that during fentanyl-pancuronium anesthesia for CABG, a heart rate (HR) increase of 28–57% above control can produce ischemia.<sup>2</sup> It thus appears that HR control is an important factor in the prevention of perioperative ischemia.

Beta-adrenergic receptor blocking drugs have greatly enhanced the management of angina pectoris. After the dangers of propranolol withdrawal were recognized, it became common practice to continue these medications up to the time of surgery and to reinstitute treatment early in the postoperative period.<sup>3,4</sup> Because of their pharmacologic properties, beta-adrenergic receptor blocking drugs could be ideal for the treatment of acute intraoperative tachycardia or hypertension, but concern for their prolonged duration of action has limited intraoperative use. Indeed, intraoperative administration of these agents can produce long-lasting cardiac depression that is additive to the cardiac depression of anesthetic agents.<sup>5</sup> Esmolol is a new intravenous beta-adrenergic receptor blocker with a distribution half-life of 2 min and an elimination half-life of 9 min.<sup>6-8</sup> The pharmacokinetics and short duration of action of the drug could make it more suitable for intraoperative use. The aims of this study were to determine the safety of various doses of esmolol during high-dose fentanyl anesthesia for myocardial revascularization and to determine its efficacy in the prevention of HR increases in response to stimulation.

### Methods

After institutional approval and written informed consent had been obtained, 37 patients scheduled for elective myocardial revascularization were entered in a double-blind study consisting of two phases.

In Phase I, 17 anesthetized patients were studied prior to surgical stimulation, and the effects of esmolol and placebo on hemodynamics were compared. In Phase II, the efficacy of esmolol in the prevention of hemodynamic responses to stimulation was compared with placebo in 20 patients. Patients with severe congestive heart failure or valvular heart disease, and those who suffered a myocardial infarction within 1 month of surgery or were not in sinus rhythm were excluded from the study.

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Premedication consisted of diazepam, 0.1 mg/kg orally 90 min before surgery, and morphine 0.1 mg/kg and scopolamine 0.4 mg im 60 min before surgery. On arrival in the operating room, a radial arterial catheter and a pulmonary arterial catheter were inserted percutaneously. ECG (lead V<sub>5</sub>) was continuously monitored. In all patients, induction of anesthesia proceeded according to the following sequence: patients were given 100% oxygen by mask and anesthesia was induced with fentanyl 75 µg/kg given over 5 to 10 min. Pancuronium 0.15 mg/kg was given in two divided doses: 1–2 mg before the fentanyl and the balance over a few min when the patient became unresponsive to verbal stimuli. Endotracheal intubation was performed after the total dose of fentanyl was administered. After intubation, the patients were mechanically ventilated to a PaCO<sub>2</sub> of 35–45 mmHg. A fractional inspired oxygen concentration (FI<sub>O<sub>2</sub></sub>) of 1.0 was used throughout the study period, and PaO<sub>2</sub> was in excess of 100 mmHg at all times. If at any time during the study period the HR dropped below 50 beats/min, the cardiac index (CI) fell below 2.0 l · min<sup>-1</sup> · m<sup>-2</sup>, or the pulmonary capillary wedge pressure (PCWP) exceeded 20 mmHg, the patient was eliminated from the study. An HR increase greater than 50% above control was another indication for termination of the study.

#### PHASE I

Seventeen patients were randomly assigned to an esmolol group (n = 9) or a placebo group (n = 8). In patients who were preoperatively receiving beta-adrenergic blocking drugs or calcium channel blocking drugs, these medications were withheld for two half-lives prior to surgery. The study drug was started 5 to 10 min following intubation.

Esmolol hydrochloride was supplied in clear glass ampuls as a 10 ml solution and was diluted in dextrose 5% to a concentration of 10 µg/ml. The placebo was dextrose 5%. Blinded solutions were provided by the hospital pharmacy for every patient. The medication was infused through a central venous catheter, using a calibrated volumetric infusion pump (IMED® 927), and in a stepwise manner to achieve an esmolol administration rate of 100, 200, and 300 µg · kg<sup>-1</sup> · min<sup>-1</sup>. Each dosage level was maintained for 10 min and was preceded by a loading dose of 500 µg · kg<sup>-1</sup> · min<sup>-1</sup> for 1.5 min. Hemodynamic measurements and blood samples for esmolol determination were obtained before anesthesia, before infusion (preinfusion baseline), at the end of each infusion level, and at 15 and 30 min after termination of the infusion. No surgical stimulation occurred during the infusion, and only saphenous vein harvesting was allowed during the postinfusion period.

#### PHASE II

Twenty patients were randomly assigned to an esmolol (n = 11) or placebo group (n = 9). For patients receiving beta-adrenergic blocking drugs or calcium channel blocking drugs preoperatively, the morning doses of these medications were withheld. Following insertion of monitoring lines, a 2-min rapid infusion of 500 µg · kg<sup>-1</sup> · min<sup>-1</sup> was given, followed by a continuous infusion of 200 µg · kg<sup>-1</sup> · min<sup>-1</sup>. Patients were then anesthetized as previously described. Complete sets of hemodynamic measurements and blood samples for esmolol determination were taken 2 min before starting the infusion, 5 min after the beginning of the infusion, and 2 min after induction, intubation, skin incision, sternotomy, and aortic root dissection. To control hypertension (mean arterial pressure > 90 mmHg), diazepam or enflurane was administered. The study was terminated when cardiopulmonary bypass was instituted.

A set of measurements included HR, mean systemic (MAP) and pulmonary artery (MPAP) pressures, PCWP, central venous pressure (CVP), and cardiac output (CO) in duplicate by thermodilution. Derived variables, including CI, stroke index (SI), left ventricular stroke work index (LVSWI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR), were calculated with standard formulae. Arterial blood was sampled at specific intervals for blood esmolol concentrations and blood gases.

Blood sampled for determination of esmolol levels was processed immediately, as the drug is rapidly metabolized by plasma pseudocholinesterases. Standard curves for esmolol and its metabolite were prepared for each patient. Following preparation the arterial samples were frozen for later analysis by high-pressure liquid chromatography (see Appendix 1).<sup>9</sup>

Statistical analysis included analysis of variance for repeated measures on each parameter. Within group differences from baseline were determined using Dunnett's multiple comparison test. Absolute changes from baseline were analyzed. Between group differences were assessed using the unpaired *t* test on the mean changes from baseline. Demographic and biochemistry data were assessed using a paired *t* test when applicable. Two-tailed null hypotheses were rejected when *P* < 0.05. Data and graphs are reported as mean ± SEM.

#### Results

The demographics and the intake of concurrent medications were comparable for the groups (table 1).

#### PHASE I (TABLE 2, FIGS. 1 AND 2)

The two groups were similar at both the awake and preinfusion baselines. During the infusion of esmolol, sig-

TABLE 1. Demographics and Concurrent Medications

	Sex (Male/ Female)	Age (yr)	History		Ejection Fraction (%)	Calcium Channel Blockers			Beta Blockers		
			Myocardial Infarction	Hypertension		D	V	N	P	M	A
Phase I											
Esmolol	8/1	62 ± 9	4	2	65 ± 14	3	1	3	2	1	1
Placebo	4/4	59 ± 5	5	5	61 ± 23	4	1	2	3	2	—
Phase II											
Esmolol	9/2	59 ± 10	5	2	72 ± 20	3	1	3	5	—	—
Placebo	8/1	59 ± 12	4	4	70 ± 11	4	—	1	6	1	1

Concurrent medications: D = diltiazem; V = verapamil; N = nifedipine; P = propranolol; M = metoprolol; A = atenolol.

nificant decreases in HR, CI, and SI, and increases in PCWP and CVP were noted. MAP, MPAP, SI, LVSWI, SVR, and PVR remained unchanged. During placebo infusion, the only significant change was a decrease in HR. The decrease in HR occurred in parallel for both groups. Differences between the esmolol and placebo groups were obtained for MPAP and PCWP at the 200 and 300

$\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  infusion levels. Both groups received comparable amounts of fluids (Normosol-R®) (esmolol =  $1045 \pm 450$  ml vs. placebo =  $1005 \pm 650$  ml). In three patients the infusion was stopped before the end of the infusion period because their CI and HR fell below the predetermined values of  $2 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  and 50 beats/min, respectively. Two of these patients were in the pla-

TABLE 2. Phase I Hemodynamics

	Awake	Preinfusion Baseline	$\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$			Postinfusion	
			100	200	300	+15 min	+30 min
HR (beats/min)							
Esmolol	64.3 ± 3.6	67.3 ± 4.1	63.1 ± 4.1	59.8 ± 3.1†	58.9 ± 3.0†	57.0 ± 3.0†	55.2 ± 3.0†
Placebo	61.1 ± 4.3	70.1 ± 4.6	66.2 ± 4.9	63.9 ± 4.0†	63.2 ± 4.0†	58.5 ± 3.4†	56.4 ± 3.1†
MAP (mmHg)							
Esmolol	96.8 ± 4.6	88.9 ± 3.3	91.8 ± 5.2	97.3 ± 9.2	89.6 ± 4.8	88.2 ± 4.8	86.7 ± 4.3
Placebo	90.9 ± 3.2	88.8 ± 3.9	85.9 ± 3.8	84.9 ± 4.4	93.0 ± 5.3	88.8 ± 4.2	86.5 ± 2.6
MPAP (mmHg)							
Esmolol	21.1 ± 3.0	15.8 ± 1.6	17.2 ± 2.5	19.3 ± 2.2‡	19.0 ± 1.8‡	17.3 ± 2.0	15.8 ± 1.9
Placebo	17.8 ± 0.8	17.1 ± 0.8	16.9 ± 0.6	16.9 ± 0.3	17.0 ± 0.9	17.4 ± 1.2	16.2 ± 0.9
PCWP (mmHg)							
Esmolol	11.1 ± 2.1	8.3 ± 1.7	10.6 ± 2.1	13.2 ± 2.0†‡	13.0 ± 1.5*‡	11.4 ± 2.0	9.9 ± 2.2
Placebo	10.9 ± 1.1	10.9 ± 1.0	10.6 ± 0.9	12.1 ± 0.6	12.5 ± 0.7	12.6 ± 0.7	11.9 ± 0.9
CVP (mmHg)							
Esmolol	5.6 ± 1.0	4.9 ± 0.9	5.7 ± 1.0	7.0 ± 0.8*	7.5 ± 1.5*	6.4 ± 1.2	5.3 ± 1.1
Placebo	7.3 ± 1.0	7.4 ± 0.9	7.8 ± 0.7	7.9 ± 1.0	7.0 ± 0.5	8.4 ± 0.7	8.5 ± 0.7
CO (l/min)							
Esmolol	4.2 ± 0.2	4.4 ± 0.3	3.8 ± 0.1	3.7 ± 0.1	3.5 ± 0.1	3.7 ± 0.2	3.8 ± 0.2
Placebo	4.0 ± 0.2	4.4 ± 0.3	4.0 ± 0.2	4.1 ± 0.3	4.0 ± 0.3	3.6 ± 0.4	3.3 ± 0.3
CI ( $1 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ )							
Esmolol	2.3 ± 0.1	2.4 ± 0.1	2.1 ± 0.1*	2.0 ± 0.1†	1.9 ± 0.1†	2.0 ± 0.1†	2.0 ± 0.1†
Placebo	2.2 ± 0.1	2.4 ± 0.1	2.2 ± 0.1	2.2 ± 0.1	2.1 ± 0.1	2.0 ± 0.2*	2.0 ± 0.1*
LVSWI ( $\text{g} \cdot \text{m} \cdot \text{m}^{-2}$ )							
Esmolol	43.0 ± 4.7	40.5 ± 3.5	36.9 ± 1.8	38.8 ± 3.2	33.8 ± 2.7	37.4 ± 2.7	39.2 ± 3.0
Placebo	39.0 ± 2.4	36.6 ± 2.8	34.5 ± 2.2	35.1 ± 3.6	37.9 ± 4.4	35.6 ± 3.9	35.8 ± 2.2
SI ( $\text{ml}/\text{m}^2$ )							
Esmolol	36.3 ± 2.3	36.7 ± 2.1	33.8 ± 1.6	34.4 ± 1.3	32.5 ± 1.6*	35.8 ± 1.1	37.4 ± 1.6
Placebo	36.2 ± 2.6	34.5 ± 2.2	33.8 ± 1.8	35.2 ± 2.6	34.1 ± 2.2	33.9 ± 2.3	35.1 ± 1.1
SVR ( $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ )							
Esmolol	1757.0 ± 67.0	1557 ± 97	1817 ± 107	1950 ± 163	1899 ± 96	1807 ± 150	1767 ± 123†
Placebo	1707.0 ± 97.6	1503 ± 58	1560 ± 60	1491 ± 49	1728 ± 69	1835 ± 103	2011 ± 226
PVR ( $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ )							
Esmolol	192.0 ± 20.6	133 ± 14	140 ± 18	132 ± 20	141 ± 25	131 ± 18	129 ± 20
Placebo	144.0 ± 23.5	117 ± 16	126 ± 12	96 ± 16	92 ± 10	109 ± 19	114 ± 21

See text for abbreviations.

Within group differences from baseline \* $P < 0.05$ ; † $P < 0.01$ .

Between group difference for mean changes from baseline ‡ $P < 0.05$ .

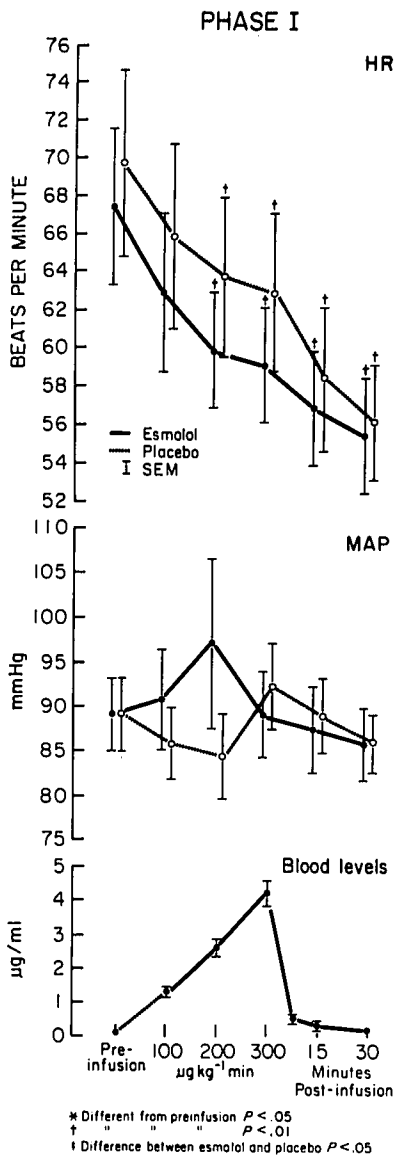


FIG. 1. Heart rate (HR) and mean arterial pressure (MAP) for esmolol and placebo group during Phase I of the study. Blood levels of esmolol in the esmolol group.

cebo group; the third patient was at the end of the 200  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  esmolol infusion. None of the patients had an HR increase of more than 50% above baseline.

No esmolol was present in the blood samples from the placebo patients. Steady-state esmolol blood levels at each dosage were found to be:  $1.25 \pm 0.25$ ,  $2.68 \pm 0.56$ , and  $4.19 \pm 1.13 \mu\text{g}/\text{ml}$  corresponding to the esmolol dosage levels of 100, 200, and 300  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively. At 5 min postinfusion, blood levels of esmolol were reduced to 8.4% of the peak levels seen at the 300  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  dose. By 30 min postinfusion, esmolol could be assayed in only four of nine patients, and those levels were less than 2% of the peak levels at 300  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ .

Some abnormal biochemistry laboratory values found in the prestudy period could be attributed to the patient's

preoperative medical condition. No significant changes were found when comparing prestudy values to poststudy values.

**PHASE II (TABLE 3, FIGS. 3 AND 4)**

In response to intubation, a significant increase in HR was observed in the placebo group, while the HR did not change significantly in the esmolol group. The differences in HR increases were statistically significant between groups at 1 and 2 min after intubation.

In the esmolol group other significant changes at various stages included reductions in MAP, PCWP, and SVR. In the placebo group, significant decreases in MAP, MPAP, PCWP, CVP, CI, and LVSWI were observed. When comparing both groups, the only other significant differences between the groups were noted for SI and LVSWI. Diazepam and enflurane were used in both esmolol and placebo groups, with no significant dose dif-

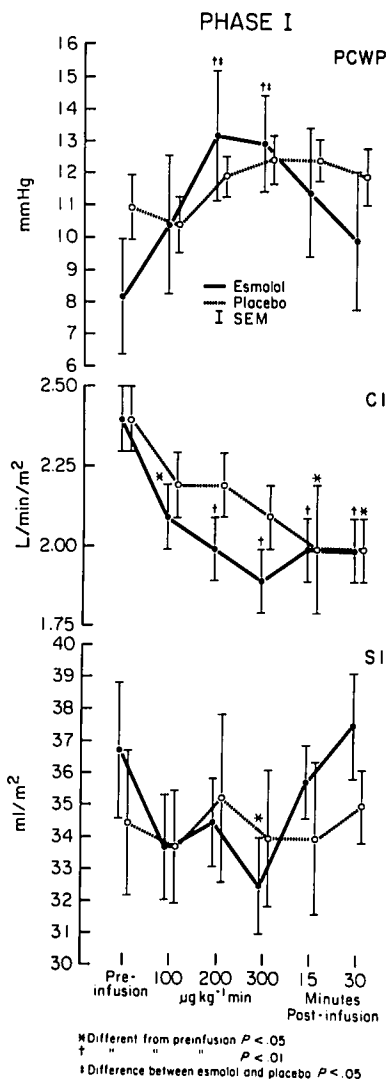


FIG. 2. Pulmonary capillary wedge pressure (PCWP), cardiac index (CI), and stroke index (SI) in both groups of patients during Phase I of the study.

TABLE 3. Phase II Hemodynamics

	Preinfusion	Preinduction	2-Min Postinduction Baseline	2-Min Postintubation	Post Skin Incision	Poststernotomy	Postaortotomy
HR (beats/min)							
Esmolol	63.9 ± 3.2	61.1 ± 3.3	63.4 ± 2.7	67.6 ± 2.9‡	61.0 ± 1.5	60.7 ± 1.7	59.1 ± 0.9
Placebo	58.4 ± 4.1	53.6 ± 3.2	61.4 ± 4.3	72.4 ± 3.4†	59.6 ± 3.8	64.7 ± 3.3*	63.6 ± 2.8
MAP (mmHg)							
Esmolol	88.6 ± 2.9	92.4 ± 4.2	84.2 ± 3.4	81.9 ± 2.4*	79.2 ± 2.6†	80.9 ± 2.9*	72.5 ± 3.3†
Placebo	88.0 ± 3.0	89.4 ± 3.1	85.9 ± 2.1	88.1 ± 2.2	81.0 ± 2.1	83.6 ± 2.0	78.6 ± 3.0*
MPAP (mmHg)							
Esmolol	19.4 ± 1.0	20.8 ± 1.2	21.8 ± 1.4	20.8 ± 1.7	17.1 ± 1.1	17.6 ± 1.7	16.8 ± 1.4
Placebo	18.4 ± 1.8	18.7 ± 1.5	20.7 ± 1.5	19.6 ± 1.6	18.2 ± 1.0	16.7 ± 0.8	14.4 ± 1.0†
PCWP (mmHg)							
Esmolol	11.0 ± 1.2	14.4 ± 1.2	14.4 ± 1.0	12.6 ± 1.0	11.2 ± 1.0	11.6 ± 1.2	11.0 ± 1.3*
Placebo	11.2 ± 1.0	12.7 ± 1.4	13.8 ± 1.4	11.8 ± 1.3	13.2 ± 1.6	9.9 ± 1.2*	8.4 ± 1.0†
CVP (mmHg)							
Esmolol	8.1 ± 0.7	9.4 ± 1.1	10.4 ± 1.3	8.6 ± 1.0	8.4 ± 1.0	7.5 ± 0.8	7.0 ± 0.9
Placebo	6.3 ± 1.2	7.3 ± 1.2	8.8 ± 1.3	7.9 ± 1.1	9.2 ± 1.4	7.3 ± 1.1	4.0 ± 0.7*
CO (l/min)							
Esmolol	4.2 ± 0.3	4.0 ± 0.2	4.7 ± 0.4	4.7 ± 0.5	4.0 ± 0.3	4.3 ± 0.4	4.2 ± 0.3
Placebo	4.7 ± 0.3	4.6 ± 0.4	4.9 ± 0.2	5.0 ± 0.1	4.1 ± 0.2	4.4 ± 0.2	4.3 ± 0.3
CI (l · min <sup>-1</sup> · m <sup>-2</sup> )							
Esmolol	2.3 ± 0.1	2.1 ± 0.1	2.5 ± 0.2	2.5 ± 0.2	2.1 ± 0.2	2.3 ± 0.2	2.2 ± 0.2
Placebo	2.5 ± 0.2	2.4 ± 0.2	2.5 ± 0.1	2.6 ± 0.1	2.1 ± 0.1	2.3 ± 0.1	2.1 ± 0.1
SI (ml/m <sup>2</sup> )							
Esmolol	36.6 ± 2.9	35.8 ± 2.8	38.8 ± 2.3	37.0 ± 2.9§	35.3 ± 2.7	38.0 ± 3.2§	37.2 ± 2.9‡
Placebo	42.4 ± 2.6	45.9 ± 4.1	42.6 ± 3.4	36.4 ± 2.5*	37.4 ± 2.6*	35.5 ± 2.6*	33.9 ± 2.0†
LVSWI (g · m · m <sup>-2</sup> )							
Esmolol	38.8 ± 3.5	37.3 ± 2.6‡	36.2 ± 1.5	35.1 ± 3.3‡	32.5 ± 2.4	36.2 ± 4.1‡	31.5 ± 2.7
Placebo	44.1 ± 2.8	47.1 ± 3.5	41.9 ± 3.7	37.8 ± 3.0*	34.0 ± 2.5†	35.3 ± 2.4†	32.6 ± 2.8†
SVR (dyn · s · cm <sup>-5</sup> )							
Esmolol	1576 ± 103	1715 ± 110	1375 ± 140*	1417 ± 181	1485 ± 101	1441 ± 114	1292 ± 118
Placebo	1438 ± 103	1503 ± 129	1281 ± 58	1300 ± 54	1398 ± 63	1420 ± 101	1406 ± 108
PVR (dyn · s · cm <sup>-5</sup> )							
Esmolol	161 ± 19	133 ± 13	128 ± 9	142 ± 21	127 ± 20	119 ± 17	115 ± 14
Placebo	122 ± 12	106 ± 15	115 ± 12	126 ± 22	120 ± 15	129 ± 18	113 ± 14

See text for abbreviations.

Within group differences from baseline \**P* < 0.05; †*P* < 0.01.

Between group differences for mean changes from baseline ‡*P* < 0.05; §*P* < 0.01.

ferences between the groups (table 4). The total dose of diazepam was 11.14 ± 5.20 mg for the esmolol group versus 14.17 ± 5.30 mg for the placebo group. Patients in the esmolol group received 0.14 ± 0.23 MAC-hours of enflurane, while the patients in the placebo group received 0.27 ± 0.35 MAC-hours (nonsignificant). Drug infusion was discontinued in two patients in the placebo group and in no patients in the esmolol group. Both patients had signs that were compatible with myocardial ischemia: one had persistent ST-segment depression with an HR of 78 beats/min and a blood pressure of 153/86; the other, who had an elevated PCWP with giant V-waves (>40 mmHg), had an HR of 48 beats/min, with frequent premature ventricular contractions and a blood pressure of 131/71. None of the patients had an HR increase of greater than 50% above baseline.

Esmolol levels at three data points were averaged for eight of 11 patients in the esmolol group. The esmolol blood levels were 2.47 ± 0.20 µg/ml postintubation, 3.10 ± 0.18 µg/ml poststernotomy, and 3.23 ± 0.33 µg/ml

postaortotomy. The levels in the placebo patients were all zero.

### Discussion

Our findings demonstrate that, under the circumstances of this study, esmolol can safely be administered during high-dose fentanyl anesthesia and that the drug is effective in blocking the HR response to intubation. The aim of the first phase of the study was to assess whether esmolol in combination with high-dose fentanyl would result in unacceptable bradycardia or myocardial depression. It has been well established that high-dose fentanyl produces bradycardia and that this HR response is secondary to stimulation of the vagal nucleus in the medulla.<sup>10</sup> This study demonstrates that the administration of esmolol to unstimulated patients receiving fentanyl and pancuronium did not produce a further reduction in HR. Whether this holds true when fentanyl is combined with other muscle relaxants remains to be proven.

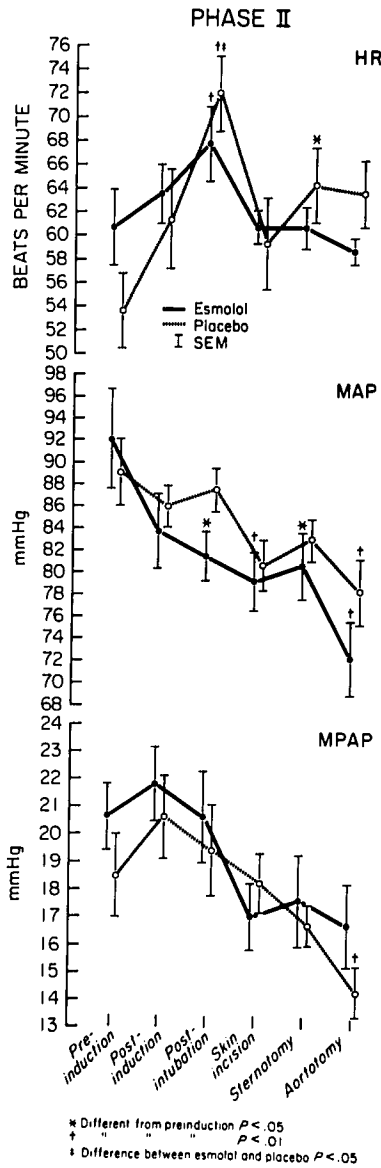


FIG. 3. Heart rate (HR), mean arterial pressure (MAP), and mean pulmonary artery pressure (MPAP) in esmolol and placebo group during Phase II of the study.

In patients anesthetized with different anesthetic agents, other investigators observed that esmolol reduced the HR in the absence of stimulation. Menkhaus *et al.* noted a reduction in HR in three groups of unstimulated patients receiving various doses of esmolol.<sup>12</sup> Similarly, Korenaga *et al.* observed a decrease in HR during infusion of esmolol at  $300 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 4 min.<sup>12</sup> The reason why these results differ from our own could be that in both of the other studies, the baseline HRs before administration of esmolol were markedly higher than in the current study, often as a result of the anesthetic technique. In the study of Menkhaus *et al.*<sup>11</sup> for instance, pancuronium was administered immediately prior to the initiation of the esmolol infusion.

The decrease in myocardial contractility produced by beta-adrenergic blocking drugs is well documented.<sup>13,14</sup>

At doses with equivalent chronotropic potency, esmolol appears to produce less myocardial depression than propranolol.<sup>8,15</sup> Nonetheless, Reves *et al.* were able to demonstrate the dose-related negative inotropic properties of esmolol in dogs anesthetized with enflurane.<sup>16</sup> In the unstimulated patients, a modest rise in PCWP and MPAP with a concomitant decrease in CI were observed at 200 and  $300 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  of esmolol. These changes, although statistically significant, do not appear to bear much clinical significance. Indeed, the changes were small, and the studied variables remained within the normal range.

Theoretically, a beta-adrenergic blocking drug could produce peripheral vasoconstriction and thus impair cardiac performance. In our study and in animal experiments, esmolol did not cause an increase in SVR. The absence of direct vasoconstrictor properties of esmolol

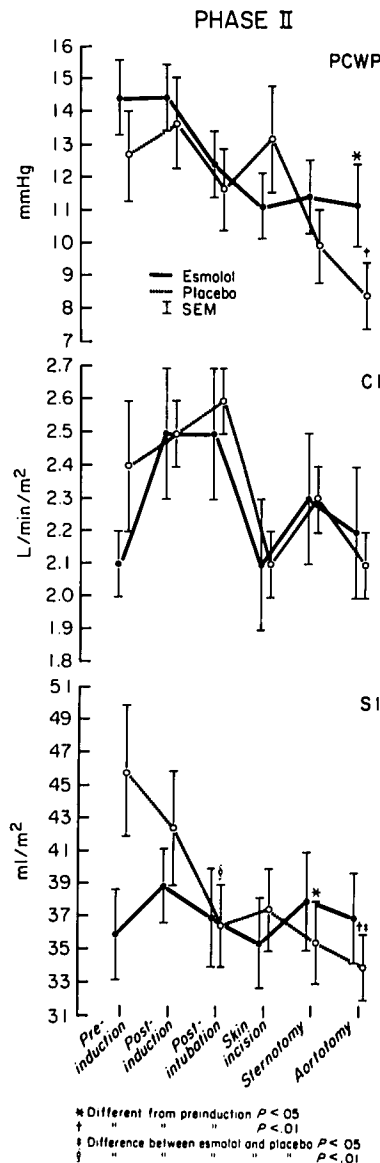


FIG. 4. Pulmonary capillary wedge pressure (PCWP), cardiac index (CI), and stroke index (SI) in both groups of patients during Phase II of the study.

TABLE 4. Supplemental Medication

	Esmolol				Placebo			
	Diazepam		Enflurane		Diazepam		Enflurane	
	n	Dose (mg)	n	Dose (MAC-hour)	n	Dose (mg)	n	Dose (MAC-hour)
Preinfusion	2	3.75	—	—	2	5	—	—
Preinduction	2	5	—	—	—	—	—	—
Induction	2	5	—	—	2	2.5	—	—
Postinduction	6	5.8	1	0.07	3	7.5	1	0.33
Postintubation	4	8.1	2	0.11	6	8.3	2	0.26
Post skin incision	3	4.17	1	0.14	4	5.04	4	0.11
Poststernotomy	2	5	7	0.11	1	7.5	4	0.24
Postaortotomy	—	—	—	—	—	—	2	0.02

n = number of patients; dose = average dose in mg for diazepam and average dose in MAC-hours for enflurane.

were demonstrated by Gorczynski *et al.*<sup>8</sup> As opposed to propranolol, esmolol did not block the decrease in diastolic blood pressure induced by isoproterenol, nor did it influence the isoproterenol-induced reduction in perfusion pressure of an isolated hindlimb perfusion model.

When the effects of esmolol were studied in a similar population during surgical stimulation (Phase II), a quite different picture emerged. Whereas the HR remained unchanged prior to stimulation, esmolol was effective in preventing the rise in HR secondary to intubation. Studies using different anesthetic techniques have shown similar results. Menkhaus *et al.*, using a diazepam-pancuronium induction, showed an attenuation of HR response to intubation, even at their lowest dose (100  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ).<sup>11</sup> Gold *et al.*, comparing esmolol to placebo, demonstrated that patients receiving esmolol at 300  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  had a significantly lower HR throughout a ketamine induction and intubation sequence than those in the placebo group.<sup>17</sup> In the study by Korenaga *et al.*, HR was significantly lower in the esmolol *versus* the placebo group after thiopental induction, although the esmolol group did have a prominent rise 3 and 5 min after intubation (70 to 85 and 86, respectively).<sup>12</sup>

In the absence of stimulation we observed no changes in blood pressure. During stimulation, blood pressure increases tended to occur and were treated with enflurane and diazepam supplements. Surprisingly, there was no difference in the amount of supplemental anesthesia used in the esmolol *versus* the placebo group. This is in contrast to other studies (Korenaga *et al.*<sup>12</sup>; Gold *et al.*<sup>17</sup>) where blood pressure was better controlled in the esmolol patients.

During the stimulated phase of the study, no difference in filling pressures or CI occurred between the groups, and the decreased SI noted in the placebo group was probably due to higher HRs during the periintubation period. As in the unstimulated phase, SVR did not increase with esmolol infusion.

The dose of esmolol that will produce effective beta blockade during anesthesia is still undetermined. Sum *et al.* demonstrated that isoproterenol-induced tachycardia can be blocked in a dose-related manner by esmolol.<sup>6</sup> At blood levels of 0.3 and 1.0  $\mu\text{g}/\text{ml}$  they produced a 50% and 80% inhibition of the isoproterenol-induced tachycardia. Using infusion rates of 50, 100, and 400  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , blood levels were 0.164, 0.6, and 1.59  $\mu\text{g}/\text{ml}$ , respectively. In contrast, Menkhaus *et al.* showed no dose-related increase in beta blockade using intubation as the standard stimulus.<sup>11</sup> With 100  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (blood level of 1.2  $\mu\text{g}/\text{ml}$ ) they had as good a clinical effect as with 400  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (blood level of 4.8  $\mu\text{g}/\text{ml}$ ). The maintenance dose that we used (200  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) to test the drug's efficacy yielded blood levels that are well within therapeutic range according to presently available evidence. Interestingly, Gold *et al.* used no loading dose prior to maintenance infusion; however, blood esmolol levels at 4 and 9 min of infusion were comparable.<sup>17</sup>

The fact that two patients in the placebo group developed evidence of ischemia, while no patients did during esmolol infusion, may be an indication that the drug provides myocardial protection. However, a greater number of patients would be required for effective comparison. Some studies indicate that esmolol limits the extent of ischemic myocardial injury.<sup>15,18</sup> Lange *et al.* induced myocardial damage by occluding the left anterior descending coronary artery in dogs and compared the effect of esmolol *versus* placebo infusion on resultant infarct size. Using tetrazoleum staining, they demonstrated a smaller area of tissue necrosis in the esmolol-treated dogs.<sup>18</sup> Further data will be required to establish whether esmolol provides myocardial protection in humans.

Assessment of the degree of beta blockade during general anesthesia is difficult and currently is being investigated.<sup>19</sup> The use of a baseline HR is unreliable in evaluating beta blockade because one does not know if a beta

blockade is adequate until stimulation takes place. Recently, in a study by Dagnino and Prys Roberts, the dose of isoproterenol required to increase the HR by 25 beats/min was used to assess the degree of beta blockade induced by different medications during anesthesia.<sup>19</sup> They concluded that this method of assessment could guide substitution therapy during the perioperative period. Esmolol has been assessed in awake patients using this technique; however, further assessment by such objective means under general anesthesia are needed to correlate more accurately the dose administered with the effect achieved.<sup>6,20</sup>

We conclude that esmolol is safe for use during anesthesia and effectively prevents the increase in HR secondary to noxious stimuli. It has the advantages of ultra-short action and improved cardioselectivity over presently available intravenous beta-adrenergic blocking drugs. Because it prevents tachycardia during stimulation, esmolol may also prevent perioperative ischemia. In doing so, the drug can potentially decrease the incidence of perioperative myocardial infarction, while its use does not appear to entail any increased risk in this group of patients with adequate left ventricular function.

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### Appendix

Blood sampled for determination of esmolol levels was processed immediately as the drug is rapidly metabolized by plasma pseudocholinesterases. An extraction was performed using methylene chloride as the organic solvent. Heparinized blood was transferred into glass tubes containing sodium fluoride, (Becton Dickinson #6470), and was thoroughly mixed. Aliquots (1 ml) were taken immediately after mixing and extracted into methylene chloride (10 ml) containing an internal marker (ASL 9038). After centrifugation at 2000 × g for 10 min, 0.5 ml of the reddish-brown aqueous phase from each tube was precipitated with perchloric acid, 0.5 ml, after the addition of another internal marker for the metabolite (ASL 8059). This precipitate was centrifuged in the same manner. Deproteinization of the red aqueous layer resulted in the production of a supernatant suitable for analysis by high-pressure liquid chromatography (HPLC). The organic phase and the aqueous supernatant were collected and stored at -20° C prior to analysis. The samples were analyzed by HPLC using a Waters® system. Recovery of the esmolol and its metabolite was quantified using a standard curve prepared from each patient's blood taken prior to anesthesia. After the addition of esmolol and its metabolite over a 500- to 1000-fold range, the standard curve samples were extracted, separated, and stored in the manner outlined previously. Determinations of recovery could then be made by comparing the samples with results obtained with aqueous standards.