Esmolol for control of increases in heart rate and blood pressure during tracheal intubation after thiopentone and succinylcholine

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Esmolol, an ultra-short-acting cardioselective beta-adrenergic blocker, was investigated in a double-blind prospective protocol for its ability to control haemodynamic responses associated with tracheal intubation after thiopentone and succinylcholine. Thirty ASA physical status I patients received a 12-minute infusion of esmolol (500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for four minutes, then 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 8 mnutes) or saline. Five minutes after the start of the drug/placebo infusion, anaesthesia was induced with 4 $mg \cdot kg^{-1}$ thiopentone followed by succinylcholine for tracheal intubation. Prior to induction esmolol produced significant decreases in heart rate (HR) (9.3 ± 1.8 per cent) and rate–pressure product (RPP) (13.1 ± 1.8 per cent), systolic blood pressure (SAP) (4.3 ± 1.5 per cent) and mean arterial blood pressure (MAP) (1.7 ± 2.0 per cent). Increases in HR, SAP and RPP after intubation were approximately 50 per cent less in patients given esmolol compared to patients given placebo. There were highly significant differences in HR ($p < 0.0001$), and RPP ($p < 0.0005$) and significant differences in SAP ($p < 0.05$) when the maximal esmolol post-intubation response was compared to the maximal placebo response. Infusion of esmolol in the dose utilized in this study significantly attenuated but did not completely eliminate cardiovascular responses to intubation.

Key words
SYMPATHETIC NERVOUS SYSTEM: sympatholytic agents, esmolol; COMPLICATIONS: hypertension, tachycardia; INTUBATION, TRACHEAL: complications.

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Esmolol is a cardioselective, beta-adrenergic blocking agent with a short duration of action because it is metabolized by a blood esterase.[1] The short duration of action permits rapid titration by intravenous infusion to a desired level of beta blockade. Likewise, cessation of esmolol infusion rapidly terminates the beta blockade.

Numerous studies have reported hypertension and tachycardia associated with laryngoscopy and tracheal intubation that may be detrimental.[2–5] Two recent studies utilized esmolol to block haemodynamic response after intubation in man following induction of anaesthesia with ketamine[6] or diazepam, N_2O (50 per cent) and pancuronium.[7] The latter study[7] was conducted in patients scheduled for elective myocardial revascularization to determine the dosage that might safely and effectively reduce cardiovascular responses to intubation. Gold *et al.*[6] found that peak heart rates and systolic pressures following intubation after ketamine induction were significantly attenuated by esmolol. Likewise, Menkhaus *et al.*[7] observed significant reductions in heart rate, mean arterial pressure and

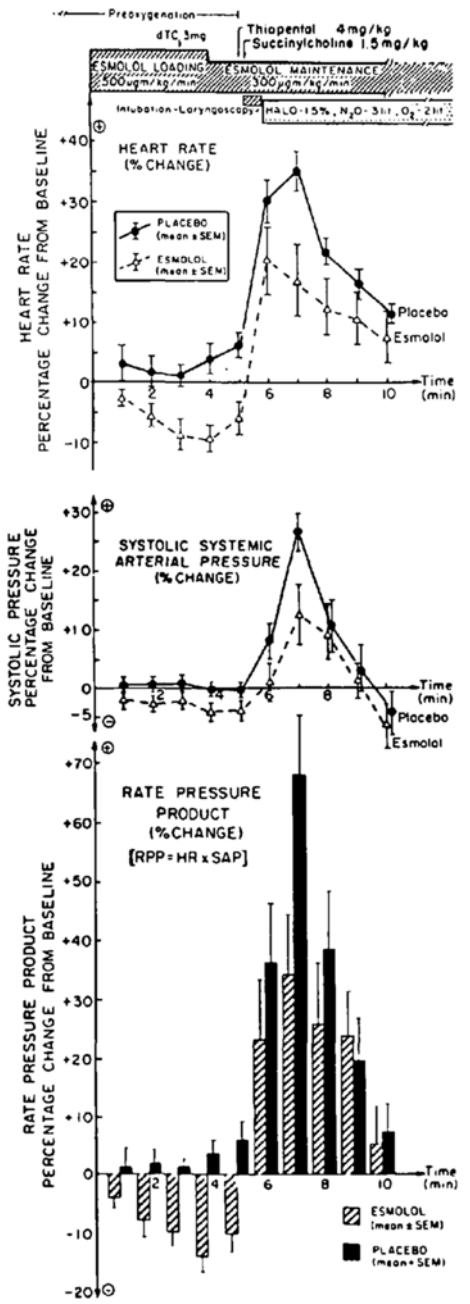

FIGURE Per cent changes in HR, SAP and RPP in esmolol and placebo treated patients.

rate pressure product at one, three and four minutes after intubation in the three esmolol treated groups in their study.

Our study was designed to investigate haemodynamic alterations following the widely utilized technique of induction of anaesthesia with thiopentone followed by succinylcholine for tracheal intubation and to evaluate the efficacy of esmolol in controlling subsequent increases in heart rate and blood pressure.

Methods

ASA physical status I patients with no history of asthma, palpatations, hypertension, cardiac conduction defects, congestive heart failure or the preoperative use of beta-blockers were included in this study. Thirty males and non-pregnant females whose mean age was 45.2 yr. (range 21 to 60 yr.) gave informed consent for the study. The study protocol was approved by the Human Studies Committee of the Brigham and Women's Hospital.

Variables monitored were pulse rate, and systolic, mean and diastolic blood pressures. Heart rate and systemic pressures were measured at one-minute intervals using an automated sphygmomanometer with strip chart recording capability (Critikon). ECG recordings were also taken using a V_5 lead.

All patients were premedicated with 10 mg of diazepam PO 60–90 minutes prior to anaesthesia. In this double-blind protocol (Figure), patients received either esmolol (American Critical Care, ASL 8052) dissolved in normal saline or an equal volume of saline by continuous intravenous infusion. After control values were obtained, infusion of either esmolol 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or saline was begun (time zero) while the patient was being pre-oxygenated. At two minutes, 3 mg of d-tubocurarine was given. At four minutes, the esmolol infusion was decreased to 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At five minutes, anaesthesia was induced with 4 $mg \cdot kg^{-1}$ of thiopentone followed by 1.5 $mg \cdot kg^{-1}$ of succinylcholine. All study patients were then intubated by the same anaesthestist, intubation being timed to last for 30 seconds. At this point, halothane 1.5 per cent, nitrous oxide (70 per cent) and oxygen (30 per cent) were begun. The esmolol infusion was continued at a rate of 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for an additional three minutes, at which point halothane was reduced to 0.5 per cent in nitrous-oxide oxygen

TABLE I Cardiovascular variables (HR, SAP, MAP, and RPP) at baseline, before and after induction, laryngoscopy and intubation (Mean ± SEM)

Protocol time	*Heart rate (HR)*		*Systolic arterial pressure (SAP)*		*Mean arterial pressure (MAP)*		*Rate pressure product (RPP = SAP × HR)*	
	Esmolol	*Control*	*Esmolol*	*Control*	*Esmolol*	*Control*	*Esmolol*	*Control*
Baseline	74.0 ± 3.2	83.6 ± 4.8	131.7 ± 4.9	131.1 ± 5.4	96.0 ± 3.3	96.1 ± 3.7	9.8 ± 0.5	10.9 ± 0.7
1 min.	71.0 ± 2.6	85.9 ± 6.2	130.1 ± 4.2	130.2 ± 6.1	93.5 ± 3.4	94.1 ± 3.7	9.3 ± 0.5	11.2 ± 1.0
2 min.	68.9 ± 2.4*	84.9 ± 5.8*	128.6 ± 4.3	130.4 ± 5.0	94.7 ± 3.0	93.8 ± 3.5	8.9 ± 0.5*	11.1 ± 0.9*
3 min.	67.2 ± 2.7†	84.2 ± 5.6†	128.0 ± 3.9	131.7 ± 5.1	93.6 ± 3.6	94.1 ± 3.3	8.7 ± 0.5§	11.1 ± 0.9§
4 min.	66.1 ± 2.1‡	86.6 ± 6.1‡	125.3 ± 3.8‡	131.0 ± 4.6‡	91.5 ± 3.2*	95.7 ± 3.2*	8.3 ± 0.4§	11.3 ± 0.9‡
5 min.	67.5 ± 2.2‡	89.0 ± 6.3‡	126.4 ± 3.8	130.6 ± 5.0	93.0 ± 3.4	95.4 ± 2.8	8.6 ± 0.5§	11.7 ± 0.9§
Induction – laryngoscopy – intubation								
6 min.	84.4 ± 3.3‡	107.4 ± 4.4‡	128.1 ± 5.2	132.7 ± 2.7	103.5 ± 4.9	108.4 ± 4.0	10.8 ± 0.6‡	13.6 ± 0.6‡
7 min.	86.2 ± 3.3‡	109.5 ± 4.5‡	143.8 ± 4.5‡	166.8 ± 9.1‡	115.8 ± 3.9	126.9 ± 7.9	12.3 ± 0.5‡	18.5 ± 1.6‡
8 min.	78.8 ± 2.4‡	99.8 ± 3.7‡	144.8 ± 5.2	146.1 ± 7.3	113.6 ± 5.0	108.1 ± 5.3	11.4 ± 0.5*	14.7 ± 1.0*
9 min.	80.3 ± 1.5†	93.4 ± 3.5†	137.8 ± 5.3	134.4 ± 5.7	107.0 ± 4.3	98.7 ± 4.4	11.1 ± 0.5	12.6 ± 0.8
10 min.	78.5 ± 1.8	89.9 ± 4.0	126.3 ± 5.3	127.2 ± 5.3	96.3 ± 3.8	94.6 ± 3.7	9.9 ± 0.5	11.2 ± 0.7

Inter-group significance level:
*$p < 0.05$; †$p < 0.01$; ‡$p < 0.005$; §$p < 0.001$.

mixture (70:30, by volume). Surgical incision occurred at least five minutes later.

Paired t-tests were used to test for significant treatment differences from the baseline clinical data. Comparisons between treatment groups for the maximum clinical measurement recorded post-laryngoscopy were made using analysis of covariance with baseline values as the covariable. Similarly, comparisons between treatment groups for the nine-minutes of the protocol were made using analysis of covariance with baseline values as the covariable. A p value of <0.05 was accepted as being statistically significant. Data are presented as means ± SEM.

Results

There were no significant differences in age (45.6 ± 2.8 and 44.9 ± 3.3 years) or weight (70.6 ± 3.6 and 64.1 ± 2.7 kg) between the two groups. Likewise, sex distribution was similar between the esmolol (14F/2M) and placebo (13F/1M) groups. The types of surgical procedures performed in the two groups were similar with a predominance of hysterectomies and gynaecological procedures.

Prior to the induction of anaesthesia, esmolol had a significant depressant effect on the heart rate (HR), systolic arterial pressure (SAP), rate pressure product (RPP), and mean arterial pressure (MAP) in comparison with patients receiving the saline control. The maximum depression occurred at minute four of the esmolol infusion, at which point HR was depressed 9.3 per cent, SAP was reduced 4.3 per cent, MAP decreased 4.7 per cent, and RPP declined 13.1 per cent (Figure). All of these changes (Table I) were statistically significant. Significant depressant changes in HR and RPP in esmolol-treated patients were observed as early as two minutes after the start of the infusion and continued until laryngoscopy. No significant change in diastolic blood pressure (DBP) was observed in either the esmolol or saline groups prior to laryngoscopy.

After the stimulation of laryngoscopy and intubation there were increases in HR, SAP, MAP, and RPP in both the esmolol treated and control groups. However, there was a significantly diminished HR response in the patients receiving esmolol (Table I) as compared to the saline control group during the first four minutes after intubation (minutes 6–9 of the protocol). For example, a 35.3 ± 6.5 per cent increase in heart rate occurred in the placebo-treated patients compared to a 17.0 ± 5.6 per cent increase in the esmolol group at two minutes after laryngoscopy (Figure). Likewise, the increase in SAP

TABLE II Maximum values following the start of laryngoscopy (Mean ± SEM)

	Esmolol group	*Control group*
HR	89.5 ± 2.9§	112.7 ± 4.2§
SAP	152.5 ± 4.8*	167.9 ± 8.3*
RPP	13.0 ± 0.5‡	18.7 ± 1.4‡
DBP	109.6 ± 3.6	112.1 ± 6.0
MAP	122.0 ± 4.0	128.9 ± 6.9

Inter-group significance level:
*$p < 0.05$; ‡$p < 0.0005$; §$p < 0.0001$.

was significantly less ($p < 0.005$) at the second minute after intubation (minute seven of protocol) in the esmolol group (13.0 ± 4.6 per cent) compared to the saline group (26.8 ± 3.6 per cent). Moreover, the increase in RPP (Table I) was significantly less in the esmolol group compared to the control groups during the first three minutes after intubation (minutes 6–8 of the protocol). There was only a 33.7 ± 9.6 per cent increase from baseline in the esmolol group compared to a 67.9 ± 9.7 per cent increase in the control group at two minutes after intubation (Figure). MAP and DBP tended to increase to the same extent in both the esmolol and saline groups. The increase in DBP was significantly less in the esmolol group compared to saline at four minutes following intubation ($p < 0.05$).

Table II presents a summary of the maximum values for HR, SAP, RPP, DBP, and MAP after the start of laryngoscopy. A significant increase in HR, SAP, and RPP occurred in both groups. However, the maximum HR, SAP, and RPP values in the control groups were significantly greater than in the esmolol treated group.

Table III presents the type and incidence of dysrhythmias noted on review of the recording of the continuous V_5 EKG following intubation. There were approximately half as many dysrhythmias seen in the esmolol group (18.8 per cent) as compared to the control group (35.7 per cent). However, this difference was not statistically significant. There were no episodes of ST depression.

Discussion

Hypertension and tachycardia subsequent to tracheal intubation have been well described.[2] In susceptible patients even this short period (2–7 minutes) of hypertension and tachycardia can result in myocardial ischaemia or increased intracranial pressure. Complications resulting from these haemodynamic events after intubation include left ventricular dysfunction,[8,9] hypertensive crises,[4] pulmonary oedema,[4] cardiac dysrhythmias,[10–12] myocardial ischaemia,[3,13] and myocardial necrosis.[3]

Roy *et al.*[3] observed myocardial ischaemia during intubation in 38 per cent of their patients with known coronary artery disease and concluded that intubation is one of the highest risk intervals in anaesthesia and surgery. Giles *et al.*[9] using radionucleotide techniques and a computerized nuclear probe in patients with coronary artery disease reported that intubation was associated with hypertension and tachycardia, increased pulmonary wedge pressures and significant decreases in left ventricular ejection fraction. In seven of 25 pa-

TABLE III Types of dysrhythmias observed in esmolol and placebo patients

Esmolol group		*Control group*	
Case no.	*Dysrhythmia*	*Case no.*	*Dysrhythmia*
#101	1° heart block	#103	Multifocal ventricular ectopy (VEBs); frequent PVCs; ventricular bigeminy
#127	Junctional premature contractions	#107	Bigeminy, sinus tachycardia, salvo of PVCs
#130	Premature ventricular contractions (PVCs)	#120	Sinus bradycardia – treated with atropine 0.4 mg IV
		#122	Bigeminy
		#125	PVCs
Incidence	(18.8%)–3/16		(35.7%)–5/14

tients, left ventricular ejection fraction did not return to preintubation values, indicating myocardial ischaemia or damage. In patients with coronary artery disease, the increase in rate pressure product, tachycardia and hypertension concomitant with intubation clearly represent a serious risk.

The risk associated with the stress of intubation, hypertension and tachycardia in the healthy individual is unknown but is assumed to be minimal. However, the presence of coronary artery disease cannot always be recognized and it would be desirable to have a technique that was innocuous enough to utilize in all patients. A particularly difficult dilemma for the anaesthetist is anaesthetizing the patient with a full stomach requiring rapid sequence ("crash") induction who may be at risk for myocardial or cerebral damage secondary to the hypertension and tachycardia that accompany these manoeuvres. Our protocol was designed to mimic a rapid sequence induction as well as elective thiopentone–succinylcholine intubation induction.

The circulatory changes seen during intubation have been ascribed to reflex stimulation of the autonomic nervous system. Plasma levels of catecholamines[14–16] and β-endorphins[16] increased during intubation in some studies. Although Dohi *et al.*[17] reported that cervical epidural blockade did not prevent haemodynamic responses to intubation, β-adrenergic blockade, especially with an ultra short-acting β-blocker such as esmolol, might attenuate these responses.

We found that esmolol was effective in limiting increases in heart rate, systolic pressure, and rate pressure product following laryngoscopy and intubation in patients in whom anaesthesia was induced with thiopentone. Esmolol did not entirely block the responses, nor did it have a significant effect on mean arterial blood pressure. However, in comparison to placebo, esmolol decreased by 50 per cent the increases in SAP, HR, and RPP associated with intubation. In addition, the incidence, duration and type of dysrhythmias subsequent to intubation were decreased in the patients, but not significantly, in patients receiving esmolol. The infusion of esmolol prior to induction did not cause haemodynamic instability, although there was a small but statistically significant decrease in HR, RPP, SAP, and MAP.

Alternative methods to attenuate the adverse response to laryngoscopy and intubation include increasing the depth of inhalation anaesthesia,[18] narcotic analgesics such as fentanyl[19–23] use of lidocaine intravenously[24–26] and topically,[27–29] vasodilating agents such as nitroprusside[30] and nitroglycerin[31,32] and other beta blockers.[33] These methods have not achieved universal popularity, nor have they been completely satisfactory. Although esmolol does not completely eliminate the cardiovascular response in the doses used in this study, it has the advantage of short duration and no clinically significant cardiovascular depression. In addition, esmolol has not been associated with complications when used with inhalation anaesthetics.[7,34,35] Our data suggest that esmolol has a predominant effect on chronotropy with little alteration in the mean arterial blood pressure. The previously described alternatives of narcotics and vasodilators have a primary effect on the blood pressure. The combination of esmolol with a narcotic or vasodilator in an attempt to attenuate all cardiovascular response to intubation warrants future investigation.

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Résumé

L'esmolol, un bloquer bêta-adrénergique cardiosélectif de courte durée d'action a été investigué dans une étude prospective à double insu pour sa capacité de contrôler les réponses hémodynamiques associées à l'intubation trachéale après thiopentone et succinylcholine. Trente patients ASA I ont reçu une perfusion de 12 minutes d'esmolol (500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ pour quatre minutes, puis 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ pour huit minutes) ou du salin. Cinq minutes après le début de la perfusion du médicament ou du placebo, l'anesthésie était induite avec 4 $mg \cdot kg^{-1}$ de thiopentone suivi de succinylcholine pour l'intubation trachéale. Avant l'induction l'esmolol a produit une diminution significative de la fréquence cardiaque (HR) (9.3 ± 1.8 pour cent) et du produit fréquence-pression (RPP) (13.1 ± 1.8 pour cent), de la tension artérielle systolique (SAP) (4.3 ± 1.5 pour cent) et de la pression artérielle moyenne (MAP) (1.7 ± 2.0 pour cent). Après l'intubation, l'augmentation dans la fréquence cardiaque, la pression artérielle systolique et la produit fréquence-pression était approximativement 50 pour cent moindre chez les patients ayant reçu de l'esmolol que chez les patients ayant reçu du placebo. Il y avait une différence hautement significative dans la fréquence cardiaque ($p < 0.0001$) et dans le produit fréquence-pression ($p < 0.0005$) ainsi qu'une différence significative dans la pression artérielle systolique ($p < 0.05$) quand la réponse maximale post-intubation à l'esmolol a été comparée à la réponse maximale au placebo. La perfusion d'esmolol aux doses utilisées dans cette étude atténue significativement mais n'élimine pas complètement les réponses cardiovasculaires à l'intubation.