The dose-related effects of bolus esmolol on heart rate and blood pressure following laryngoscopy and intubation

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Introduction

The cardiovascular responses to laryngoscopy and intubation include transient increases in blood pressure and heart rate. Patients with coronary artery disease, a recent myocardial infarction, hypertension, preeclampsia, or cerebrovascular disease, such as tumors, aneurysms, or increased intracranial pressure, have increased morbidity and mortality if their heart rate and blood pressure increase during laryngoscopy and intubation. This increase in blood pressure and heart rate, although transient, may be detrimental to some patients undergoing laryngoscopy and intubation. The anesthesia provider must be aware of various methods to blunt this response to laryngoscopy and intubation. Esmolol has proven effective to blunt this response.

The peak effect of esmolol is 2 minutes from the time of intravenous (IV) administration. It is metabolized by esterases in the cytosol of the red blood cells, resulting in a short duration of action (10-15 minutes). These characteristics make esmolol a useful drug to blunt the increase in heart rate and blood pressure that occurs during the stimulating events associated with the induction of general anesthesia.

Esmolol should be used with caution in some

Many researchers have studied esmolol and its effects on heart rate and blood pressure. All studied relatively large doses of esmolol. Therefore, the purpose of the present study was to determine whether small doses of esmolol would blunt the transient increases in blood pressure and heart rate caused by laryngoscopy. This double-blind, prospective, randomized study included 61 subjects. The subjects were randomized to 1 of 3 groups: group 1 received esmolol, 0.2 mg/kg; group 2 received esmolol, 0.4 mg/kg; and group 3 received saline placebo.

Groups 1 and 2 had smaller increases in heart rate than group 3. We also found that the 0.4 mg/kg dose significantly blunted the increase in mean arterial pressure seen in group 3. This study shows that small doses of esmolol may block the increases in heart rate and blood pressure resulting from laryngoscopy and intubation.

Key words: Blood pressure, esmolol, heart rate, laryngoscopy.
patients. Since the cardioselective β-adrenergic blocker effects of esmolol are not absolute, it should be used with caution in patients with bronchospastic disease. The use of esmolol may result in hypotension in some patients. Also, esmolol may exacerbate symptoms of cardiac failure in patients who are in congestive heart failure. Smaller doses of esmolol must be studied in the hope that these adverse effects will be less.

In a study by Sheppard et al, the effects of 100 to 200 mg of bolus esmolol were examined. Their study included 45 patients undergoing intubation for surgery. The heart rate decreases were significant at 1 minute for both the 100-mg and 200-mg groups compared with the placebo group. Heart rate decreases were greater in the 200-mg group and lasted for a longer time. Decreases in systolic blood pressure were reported for both esmolol groups. Again, the 200-mg group had a significantly greater reduction in systolic blood pressure. Withington et al showed that bolus doses of esmolol, 1.5 mg/kg, abate hypertension and tachycardia.

Amelioration of the tachycardia associated with intubation was studied by Öxorn et al using bolus doses of 100 to 200 mg of esmolol. Both groups had decreases in heart rate responses to intubation compared with the placebo group. The decrease in heart rate was equally effective in both groups. Neither group of patients who received esmolol had ablation of the hypertension seen with intubation.

Anesthesia providers have a host of pharmacological agents to use to attenuate the cardiovascular responses to sympathetic tone-mediated increases in heart rate and blood pressure. Choosing the most effective agent depends on each patient’s history. Helfman et al studied fentanyl, lidocaine, and esmolol for their effectiveness. Doses of 200 µg of fentanyl, 200 mg of lidocaine, or 150 mg of esmolol or placebo were given to 80 patients before the induction of anesthesia. Standard induction doses of thiopental and succinylcholine were given with time allotted for distribution. Intubation of the trachea was accomplished with 1 minimum alveolar concentration of isoflurane and 60% nitrous oxide. The placebo group had a 44% increase in heart rate, the lidocaine group had a 51% increase, the fentanyl group had a 37% increase, and the esmolol group had an 18% increase in heart rate. Esmolol was consistent in protecting against heart rate increases during laryngoscopy and intubation. The researchers recommended that esmolol be given 2 minutes before intubation. Jacque et al recognized the successful use of esmolol during the induction of anesthesia. This group of researchers suggested that timing is everything, and 2 minutes before induction is effective, whereas 3 to 4 minutes before induction overshoots the effective phase of the β antagonistic properties of esmolol.

Jacque et al conducted another study using single-bolus esmolol 2 minutes before intubation. Results once again suggested that 2 minutes must elapse to allow for maximum β blockade. No adverse effects, such as hypotension or bronchospasm, were seen with a 150-mg bolus dose of esmolol. If adverse effects had occurred, the dissipation of esmolol in 15 minutes makes it advantageous compared with longer acting β-blockers.

The Canadian Multicentre Trial, conducted by Miller et al, studied the hemodynamic responses to tracheal intubation in 545 patients. Dose-response and adverse effects of esmolol were reviewed. Patients were divided into 3 groups: group A received esmolol 100 mg, IV bolus; group B received esmolol 200 mg, IV bolus; and group C received a placebo. The study protocol was as follows: the control drug was administered, followed by thiopental, 3 to 5 mg/kg; succinylcholine, 1.5 mg/kg; and fentanyl, 2 to 3 or 4 to 5 µg/kg. Some patients received no narcotic before induction. This study revealed that patients receiving 100 mg or 200 mg of esmolol had less heart rate response to tracheal intubation than those in the groups receiving placebo or no narcotic. The latter groups also sustained increases in systolic blood pressure. The doses of 100 mg and 200 mg of esmolol reduced heart rate increases compared with placebo, but the groups receiving esmolol did not experience a difference in the heart rate control due to the amount of drug given.

Control of systolic blood pressure when using esmolol alone was not effective. A blunting of systolic blood pressure increases occurred when using esmolol along with low-dose narcotics. When moderate doses of narcotics were used, systolic blood pressure decreases were noted in all 3 groups. The occurrence of adverse effects, such as pain at injection site, bradycardia, and bronchoconstriction, was comparable to that in the placebo group.

When using higher doses of esmolol (200-mg IV bolus) with a moderate-dose narcotic (4-7 µg/kg fentanyl) the chronotropic response to intubation was lowered, as was the blood pressure.
After administration of thiopental, blood pressure was significantly decreased, making this combination of 200 mg of esmolol, 4 to 7 µg/kg of fentanyl, and thiopental for induction problem-ridden. Therefore, the Canadian Multicentre Trial found that a 100-mg IV bolus of esmolol controls heart rate increases during intubation. When combined with low-dose narcotic, esmolol can help attenuate both systolic blood pressure and heart rate increases accompanying tracheal intubation. The study also gives an alternative, such as the combination of esmolol with narcotics, to enable the administration of a smaller dose of narcotic, therefore, diminishing the unwanted adverse effects of high-dose narcotics. Gold and Elliott reviewed the clinical applications of using esmolol during induction of anesthesia to abate the hypertension and tachycardia often associated with tracheal intubation. Esmolol, 500 µg/kg, was given by IV bolus followed by an infusion of 300 µg/kg. This esmolol regimen was given to 185 patients undergoing general anesthesia. The group receiving esmolol had heart rates greater than 100 beats per minute 26% of the time during induction events, whereas the placebo group had heart rates greater than 100 beats per minute 73% of the time. This is important because patients at risk for perioperative myocardial ischemia may have a postoperative myocardial infarction if heart rates of greater than 100 beats per minute occur for a sustained period. This finding emphasizes the importance of controlling the myocardial oxygen supply and demand, of which heart rate is the principal determinant.

Whether to give esmolol by bolus rather than as a continuous infusion has been studied extensively. Many proponents of the bolus method argue the time, expense, and trouble of mixing infusions can be avoided, especially when short-term therapy is the goal. Mallon et al studied whether bolus doses of esmolol as opposed to a continuous infusion of esmolol would bring the same effective attenuation of hemodynamic response to intubation. The simpler technique of esmolol by IV bolus involved giving 100 or 200 mg of esmolol or placebo 90 seconds before intubation. Forty-five patients were studied using a rapid-sequence induction with thiopental, 3 to 5 mg/kg; succinylcholine, 1.5 mg/kg, also was used. Esmolol was ineffective at protecting all cardiovascular response to intubation in 27% of the patient population. It is well to remember no narcotics were used. Both doses of esmolol blunted heart rate by 34% and 71%, respectively, for rate pressure product. The importance of rate pressure product and its relationship to global myocardial oxygen consumption has been shown to have a significant correlation. Blood pressure increases were not altered in the study. Bernstein et al studied the effects of bolus esmolol and found a 30% reduction in the increase in heart rate during rapid-sequence induction.

The studies reviewed used a wide range of esmolol. Doses of 0.4 to 4 mg/kg were used. The other agents used in the studies ranged from low-dose narcotic to moderate-dose narcotic to no narcotic. Some studies used benzodiazepines, whereas others did not. Also, bolus administration vs infusion of esmolol was studied for effectiveness in decreasing heart rate and blood pressure during induction.

A variety of induction protocols were used. Most were of a rapid-sequence variety using thiopental and succinylcholine, with varying time lapses for infusion of esmolol, hypnotic, muscle relaxant, and actual intubation. Some studies used oxygen and nitrous oxide with isoflurane after intubation of the trachea. Others used only oxygen. One study used vecuronium, 5 mg, after a rapid-sequence protocol using control drug, thiopental, and succinylcholine. The objective was to not cloud the results with other adrenergic antagonistic agents.

These studies show that esmolol alone is not consistently effective for blocking the cardiovascular response during induction. The studies reviewed do not show whether there is a minimal effective dose when used in conjunction with other standard induction protocols that will protect patients from transient increases in heart rate and blood pressure. Therefore, the purpose of the present study was to determine whether smaller doses of esmolol would blunt the transient increases in blood pressure and heart rate caused by laryngoscopy and intubation.

Materials and methods

This double-blind, prospective, randomized study included 61 subjects. The study was approved by the institutional review board before the collection of data. The inclusion criteria were patients aged 18-60 years, ASA physical status I or II, with no history of cardiovascular problems who were scheduled to undergo general anesthesia requiring laryngoscopy and placement of an endotracheal tube. The exclusion criteria were as fol-
adolescents: pregnancy; patients unable to understand or follow instructions; history of asthma, chronic obstructive pulmonary disease, or bronchospasm; history of heart conduction disturbances; concurrent drug therapy with β-adrenergic blockers, β-adrenergic stimulants, α-adrenergic blockers, α-adrenergic stimulants, antiarrhythmics, digoxin, adrenergic augmenting psychotropic drugs, reserpine, guanethidine, or calcium channel blockers; weight less than 50 or greater than 100 kg; and a resting heart rate less than 60 beats per minute.

After obtaining written informed consent, the subjects were randomized to 1 of 3 groups: group 1 received esmolol, 0.2 mg/kg (n = 20); group 2 received esmolol, 0.4 mg/kg (n = 21); and group 3 received saline placebo (n = 20). Each subject received a premedication dose of IV midazolam that did not exceed 0.02 mg/kg. The baseline blood pressure and heart rate were recorded. Following this, the subject was preoxygenated with 100% oxygen via mask, and a defasciculating dose of a nondepolarizing muscle relaxant was administered. Each subject received fentanyl, 2 µg/kg IV, followed by the randomized dose of the test medication mixed in 10 mL of saline. General anesthesia was induced with sodium thiopental, 4 mg/kg, over 15 seconds. Muscle relaxation was provided by succinylcholine, 1.5 mg/kg, over 15 seconds. The anesthesiologist was instructed to wait for 60 seconds following the administration of sodium thiopental before performing laryngoscopy and intubation. Laryngoscopy was performed within 30 seconds. After intubation, the subject received nitrous oxide and oxygen in a 60/40 ratio and isoflurane, 0.5% or less. The subject’s blood pressure and heart rate were recorded at 30 seconds, 2 minutes, and 5 minutes after intubation. The data as a percentage of baseline were analyzed using repeated measures. Adjustments were made for multiple comparisons using the Fisher protected least significant difference with Bonferroni correction as appropriate.

**Results**

Groups 1 and 2 had smaller increases in heart rate than group 3. The smaller heart rate increases in groups 1 and 2 compared with group 3 were statistically significant at 30 seconds (P=.0001 for both comparisons) and 2 minutes (0.2 mg/kg, P=.0002 and 0.4 mg/kg, P=.0005). Group 1 had a significantly decreased heart rate at 5 minutes (P=.0293) compared with group 3. Group 2 showed a statistically significant smaller increase in mean arterial pressure (MAP) at 30 seconds (P=.0057) and 2 minutes (P=.0107) compared with group 3, but no significant difference was noted at 5 minutes (P=.2081). No significant differences in MAP were found between group 1 and group 3. Tables 1 and 2 provide the summary statistics for these data.

This study showed that esmolol at doses of 0.2 and 0.4 mg/kg resulted in a significantly smaller increase in heart rate following laryngoscopy and intubation compared with a placebo (Figure 1).

### Table 1. Heart rate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time, min</th>
<th>n</th>
<th>Mean</th>
<th>SEM*</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Baseline</td>
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<td>84.9</td>
<td>2.9</td>
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<tr>
<td></td>
<td>0.5</td>
<td>20</td>
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<td>2.8</td>
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<td></td>
<td>2.0</td>
<td>20</td>
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<td>Baseline</td>
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<td>88.2</td>
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<td>21</td>
<td>82.7</td>
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<tr>
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<td>Baseline</td>
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<td>75.1</td>
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<tr>
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<td>5.0</td>
<td>20</td>
<td>83.7</td>
<td>2.5</td>
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</table>

*SEM indicates standard errors of the means.

### Table 2. Mean arterial pressure: means and standard errors of the means (SEM)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time, min</th>
<th>n</th>
<th>Mean</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esmolol</td>
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<td>90.6</td>
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<tr>
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<td>0.5</td>
<td>20</td>
<td>110.3</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
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<td>5.0</td>
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<td>79.9</td>
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<td></td>
<td>Baseline</td>
<td>21</td>
<td>85.8</td>
<td>2.4</td>
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<tr>
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<td>95.4</td>
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<td></td>
<td>2.0</td>
<td>21</td>
<td>85.8</td>
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<td></td>
<td>5.0</td>
<td>21</td>
<td>77.7</td>
<td>2.7</td>
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<tr>
<td>Saline</td>
<td>Baseline</td>
<td>20</td>
<td>94.5</td>
<td>2.3</td>
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<tr>
<td></td>
<td>0.5</td>
<td>20</td>
<td>120.4</td>
<td>2.7</td>
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<td>5.0</td>
<td>20</td>
<td>89.7</td>
<td>3.9</td>
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</table>
Figure 1 shows that group 3 had a peak increase in heart rate of 40% at 0.5 minutes. In comparison with the group 3, groups 1 and 2 had heart rate increases that were less than 20%. Group 2 had the lowest increase in heart rate. Neither of these doses of esmolol completely blunted the heart rate response to laryngoscopy and intubation.

Comparison of groups 2 and 3 showed that the 0.4-mg/kg dose significantly blunted the increase in MAP (Figure 2). The MAP of the subjects in group 2 increased 12% at 0.5 minutes after intubation, while in group 3, the increase was 28%. Figure 2 shows that the MAP of the subjects in group 2 returned to baseline in 2 minutes following intubation.

Discussion
Patients with a history of cardiovascular disease and certain neurologic diseases who require general anesthesia may benefit from a reduction in the elevation in heart rate and MAP associated with laryngoscopy and intubation. These patients may be at risk for complications, such as myocardial ischemia, heart failure, and dysrhythmias. Patients with intracranial lesions, aneurysms, and vascular disease exposed to significant transient increases in blood pressure can have irreversible damage.

The smaller doses of esmolol administered in the present study did not completely block the increase in heart rate or MAP that occurs after intubation. The observed increases in heart rate and MAP after intubation were less than 20% over baseline values. Further study is needed to determine the minimum esmolol dose needed to completely blunt the cardiac stimulation associated with airway manipulation.

The present study included healthy subjects. Therefore, the results cannot be generalized to patients with cardiovascular disease. A study by Kanitz et al of intraoperative use of bolus doses of esmolol to treat tachycardia included 1 subject who was receiving clonidine for the control of hypertension. This subject became hypotensive following a 50-mg bolus of esmolol. The researchers stated that this was easily corrected with ephedrine. The doses of esmolol (0.04 and 0.02 mg/kg) used in the present study were equal to 28 and 14 mg, respectively, in the average 70-kg person. These doses are much smaller than the dose administered by Kanitz et al. Therefore, the smaller doses may have less potential for producing hypotension in similar patients.

There were no adverse outcomes noted in the present study. This lack of adverse effects may be related to the small dose of esmolol administered or the subjects chosen to participate in the study. The use of smaller doses of esmolol in patients with cardiovascular disease will need to be addressed in a separate study.

Future studies will need to focus on the use of esmolol to control the heart rate and blood pressure throughout the entire perioperative period. Maintaining a tight control on the heart rate and MAP after intubation was successful in the present study.

Figure 1. Changes in heart rate as a percentage of baseline

![Figure 1](image)

Figure 2. Changes in blood pressure as a percentage of baseline

![Figure 2](image)

$P < .05$ for 0.4 mg/kg esmolol vs saline. $P < .05$ for 0.2 mg/kg esmolol vs saline.
rate and blood pressure of the patients in the subgroup who are at risk for increased morbidity and mortality may significantly decrease the morbidity and mortality in this group.

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