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Comparison of the effects of intravenous alfentanil and esmolol on the cardiovascular response to double-lumen endobronchial intubation

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Summary

We compared the effect of alfentanil 10 $\mu g.kg^{-1}$ and esmolol 1.5 $mg.kg^{-1}$ on the cardiovascular responses to laryngoscopy and double-lumen endobronchial intubation in two groups of 20 ASA 2–3 patients undergoing pulmonary surgery, in a randomised double-blind study. Arterial pressure and heart rate decreased after induction of anaesthesia and increased after intubation in both groups ($p < 0.05$) but remained at or below baseline values, and changes were comparable in both groups. Plasma catecholamine concentrations decreased after induction of anaesthesia in both groups ($p < 0.05$). Epinephrine concentrations increased in the esmolol group after intubation ($p < 0.05$) but remained below baseline in the alfentanil group ($p < 0.05$). Norepinephrine concentrations increased significantly in both groups after intubation but were higher in the esmolol group ($p < 0.05$). Although both esmolol 1.5 $mg.kg^{-1}$ and alfentanil 10 $\mu g.kg^{-1}$ similarly attenuated the arterial pressure and heart rate response to endobronchial intubation, plasma catecholamine concentrations increased in the esmolol group to values greater than previously reported after tracheal intubation.

Keywords *Intubation*: endobronchial. *Sympathetic nervous system*: β adrenergic antagonists; esmolol. *Analgesics*: alfentanil.

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Laryngoscopy and intubation with a double-lumen endobronchial tube is accompanied by increased heart rate, arterial blood pressure and plasma catecholamine concentrations [1], mediated by increased sympathetic nervous activity [2, 3]. The increases in heart rate and arterial pressure are of similar magnitude and duration to the well-described responses to laryngoscopy and tracheal intubation, i.e. mean increases of 15–20 $beats.min^{-1}$ and 30–40 mmHg, respectively, for approximately 5–6 min. These responses may result in myocardial ischaemia in susceptible individuals [4], and patients presenting for surgery which requires double-lumen endobronchial intubation (mostly pulmonary surgery) are a high-risk group for coexisting ischaemic heart disease. We have previously shown that the haemodynamic changes to double-lumen endobronchial intubation were attenuated by the administration of intravenous esmolol 1.5 $mg.kg^{-1}$ [1]. However, plasma norepinephrine concentrations were significantly increased after intubation in those who received esmolol compared with control subjects, suggesting that although esmolol diminished the end-organ response to intubation, sympathetic nervous system activity was increased. This may be because esmolol, by decreasing the haemodynamic changes, prevented a baroreflex-mediated inhibition of central sympathetic activity, which occurred in the control group.

Several drugs have been shown to attenuate the cardiovascular responses to laryngoscopy and intubation [3] and intravenous opioids, e.g. alfentanil [5, 6], are commonly used. However, there are few data regarding the effects on

plasma catecholamine concentrations after endobronchial intubation, and no data comparing the effects of different drugs. Alfentanil has a similar onset and duration of action [7] to esmolol. We therefore performed a double-blind study to compare the effects of esmolol and alfentanil on the cardiovascular and catecholamine responses to laryngoscopy and endobronchial intubation.

Methods

After obtaining Local Research Ethics Committee approval and written informed consent, 40 adult patients (ASA grades 2–3) undergoing elective pulmonary surgery requiring endobronchial intubation were studied. Patients with the following were not studied: arterial hypertension (diastolic pressure >90 mmHg), hiatus hernia or symptomatic reflux, obesity, suspected difficulty in intubation, asthma, known hypersensitivity to beta-blockers or opioids, electrocardiography (ECG) evidence of heart block, or the presence of a cardiac pacemaker. Patients were allocated at random, using a sealed envelope technique, to receive either alfentanil 10 $\mu g.kg^{-1}$ or esmolol 1.5 $mg.kg^{-1}$. The study drugs were diluted to a volume of 10 ml with saline and were prepared by a third party so that the investigators were unaware of their identity. All patients were premedicated with lorazepam 30–40 $\mu g.kg^{-1}$ approximately 2 h before induction of anaesthesia.

After insertion of intravenous and radial artery cannulae under local anaesthesia (lidocaine 1%), an intravenous infusion of compound sodium lactate solution at approximately 20 $ml.min^{-1}$ was started. Pulse oximetry, ECG (leads II and V_5) and arterial pressure monitoring were commenced. The patients' lungs were pre-oxygenated for 2 min, during which time arterial blood was obtained for measurement of catecholamine concentrations. Anaesthesia was then induced (at $t = 120$ s) with intravenous thiopental 3–5 $mg.kg^{-1}$ and vecuronium 0.1 $mg.kg^{-1}$ was administered to produce neuromuscular blockade. The patients' lungs were then ventilated with isoflurane 1% and nitrous oxide 50% in oxygen, maintaining end-expiratory carbon dioxide tension at 4.0–4.5 kPa. Two minutes after induction ($t = 240$ s), the study drug was administered intravenously over 30 s. Two minutes later ($t = 360$ s), laryngoscopy and endobronchial intubation were performed using a 37 FG or 39 FG endobronchial tube (Mallinckrodt (UK) Ltd, Bicester, Oxon) as appropriate. All intubations were performed by the same anaesthetist (K.J.W.). Duration of laryngoscopy (defined as the time from the start of laryngoscopy to inflation of the bronchial cuff) and any difficulties were noted.

Systolic, mean and diastolic arterial pressures, heart rate and arterial oxygen saturation (S_pO_2) were recorded at 30-s intervals from the start of pre-oxygenation until 5 min after intubation. Further arterial blood samples were obtained for analysis of plasma catecholamine concentrations at 1 min before and 1, 3 and 5 min after intubation. The samples were placed immediately on ice and plasma was separated by centrifugation at 2000 r.p.m. for 3 min, within 20 min of collection. Plasma was stored at -70 °C pending analysis by reverse-phase high-pressure liquid chromatography with electrochemical detection as previously described [1]. Inter- and intra-assay coefficients of variation were, respectively, 2.10% and 4.90% for epinephrine and 2.94% and 4.14% for norepinephrine, with a lower level of sensitivity of 0.2 $pmol.ml^{-1}$. Escape medication comprised ephedrine 3 mg increments for hypotension (systolic pressure <80 mmHg for >60 s), atropine 0.6 mg for bradycardia (heart rate <40 $beat.min^{-1}$) and either hydralazine 5 mg increments or glyceryl trinitrate 0.2 mg increments for hypertension (systolic pressure >200 mmHg for >60 s).

Power analysis based on previous data [1] showed that 19 patients per group would be required to detect a difference in mean arterial pressure of 15 mmHg between the groups after intubation ($\beta = 0.2$, $\alpha = 0.05$). Statistical analysis was performed using general linear model analysis of variance for repeated measures (with time and treatment group as the within- and between-group factors, and post-test analysis with Bonferroni adjustment) using the computer programme SPSS for Windows (release 8.0, 1997).

Table 1 Patients' characteristics, dose of thiopental and time to successful endobronchial intubation in patients receiving either alfentanil or esmolol before endobronchial intubation. Values are mean (SD).

	Alfentanil ($n = 20$)	Esmolol ($n = 20$)
Age; years	59.1 (12.3)	54.8 (15.4)
Sex; M:F	13 : 7	14 : 6
Weight; kg	73.0 (10.4)	66.4 (12.8)
Pre-operative SAP; mmHg	140.2 (23.2)	148.6 (22.3)
Pre-operative DAP; mmHg	76.5 (8.3)	76.1 (11.4)
Dose of thiopental; mg	310.0 (46.2)	277.5 (47.2)
Time to intubation;* s	19.5 (11.0)	23.4 (7.8)

*Time from start of laryngoscopy to inflation of the bronchial cuff. SAP = systolic arterial pressure; DAP = diastolic arterial pressure (measured the day before surgery).

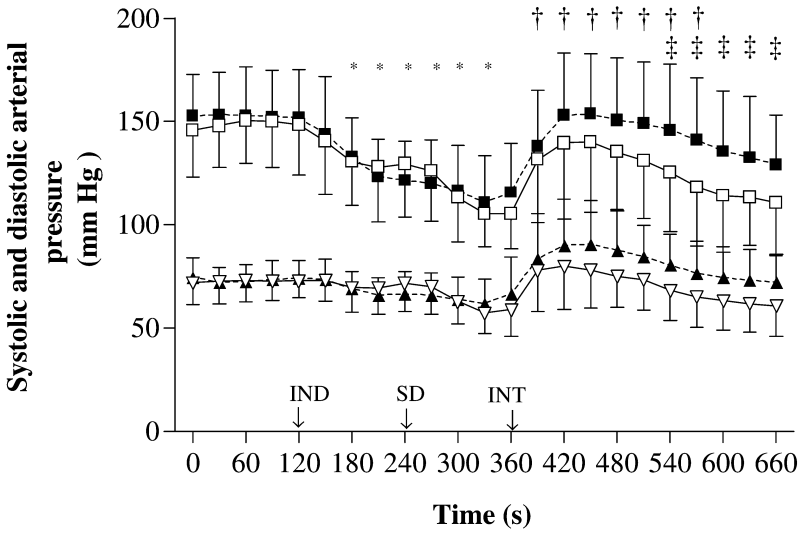

Figure 1 Systolic and diastolic pressures in patients receiving alfentanil (□ and ▽, respectively) or esmolol (■ and ▲, respectively) during induction of anaesthesia (IND), administration of study drug (SD) and endobronchial intubation (INT). Values are mean (SD). *$p < 0.05$ within groups compared with baseline; †$p < 0.05$ within groups compared with pre-intubation; ‡$p < 0.05$ between groups.

Results

Patients' characteristics and induction dose of thiopental were similar between the groups (Table 1). No difficulties were encountered during endobronchial intubation and the times to successful intubation were comparable.

Arterial pressure decreased after induction of anaesthesia, and increased after laryngoscopy and endobronchial intubation in both groups (Figs 1 and 2). Heart rate was stable after induction of anaesthesia and decreased slightly after administration of both study drugs, but was significantly slower before, and during the first 3 min after, laryngoscopy and intubation in the esmolol group (Fig. 3). Overall, increases in heart rate and arterial pressure after intubation were relatively modest and remained at or below baseline values throughout the study period. Epinephrine concentrations decreased significantly after induction of anaesthesia in both groups but increased significantly after intubation in the esmolol group (Fig. 4). Plasma norepinephrine concentrations remained unchanged after induction of anaesthesia, but increased significantly in both groups after laryngoscopy and intubation (Fig. 5). The increase in norepinephrine concentrations was significantly greater in the esmolol group compared with the alfentanil group. One patient in the alfentanil group and two in the esmolol group recorded transient (< 60 s) systolic pressures above 200 mmHg but no escape medication was required. Hypotension requiring escape medication occurred in two patients in the alfentanil group and one patient in the

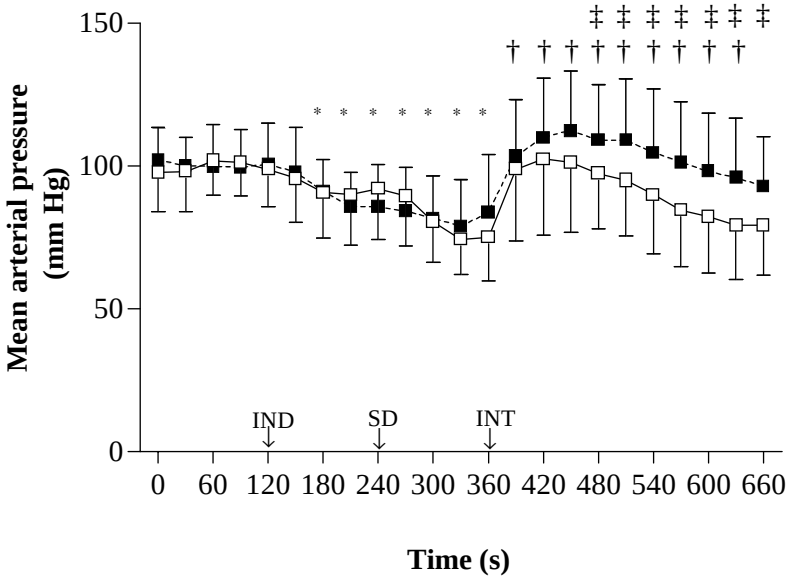

Figure 2 Mean arterial pressure in patients receiving alfentanil (□) or esmolol (■) during induction of anaesthesia (IND), administration of study drug (SD) and endobronchial intubation (INT). Values are mean (SD). *$p < 0.05$ within groups compared with baseline; †$p < 0.05$ within groups compared with pre-intubation; ‡$p < 0.05$ between groups.

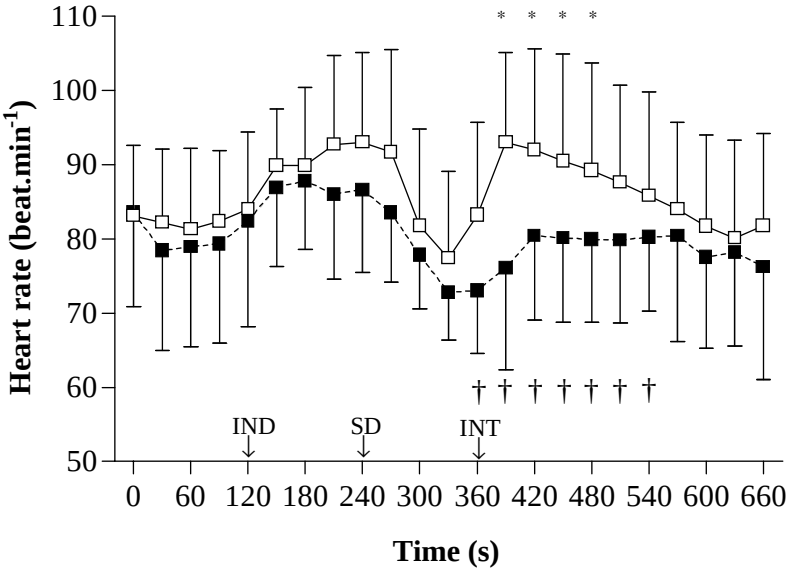

Figure 3 Heart rate during induction of anaesthesia (IND), administration of study drug (SD) and endobronchial intubation (INT) in patients receiving alfentanil (□) or esmolol (■). Values are mean (SD). *$p < 0.05$ within groups compared with pre-intubation; †$p < 0.05$ between groups.

esmolol group. One patient in the alfentanil group and one patient in the esmolol group had frequent atrial ectopic beats following intubation. Another patient in the alfentanil group, who had longstanding atrial fibrillation and 1-mm depression of the ST segment before induction of anaesthesia, developed a 2-mm increase in ST segment depression following intubation. These ECG changes were of short duration and resolved spontaneously in all cases.

Discussion

In this study, alfentanil 10 $\mu g.kg^{-1}$ and esmolol 1.5 $mg.kg^{-1}$ given intravenously had similar effects on arterial pressure and heart rate when administered 90 s before laryngoscopy and endobronchial intubation. Arterial pressure increased transiently after intubation, subsided within 5 min, and was comparable to previous data. Plasma catecholamine concentrations increased significantly above baseline only in the esmolol group.

Previous studies in this field have varied in their methodology, definitions of hypo- and hypertension, the doses of drug and techniques used, and in the timing and interpretation of the data presented [3]. In studies using thiopental for induction of anaesthesia, mean arterial pressure increased at intubation by approximately 40–50 mmHg, or 30% compared with baseline pre-induction values [2, 8, 12]. In a previous study, using similar methodology, arterial pressure increased after intubation by approximately 50 mmHg to mean values

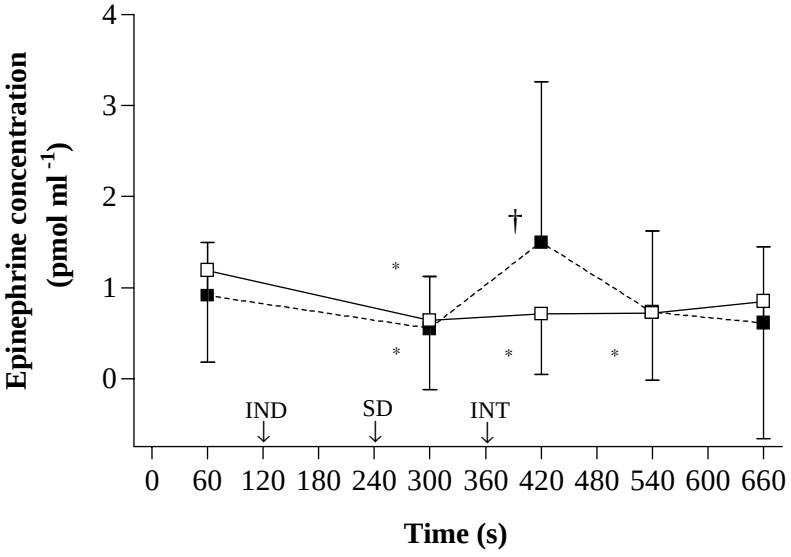

Figure 4 Plasma epinephrine concentrations during induction of anaesthesia (IND), administration of study drug (SD) and endobronchial intubation (INT) in patients receiving alfentanil (□) or esmolol (■). Values are mean (SD). Epinephrine concentrations decreased after induction of anaesthesia in both groups (*$p < 0.05$ compared with baseline), but increased after intubation in the esmolol group only (†$p < 0.05$, within-group comparison). Epinephrine concentrations after intubation were higher in the esmolol group, although the difference was not statistically significant ($p = 0.058$ between groups).

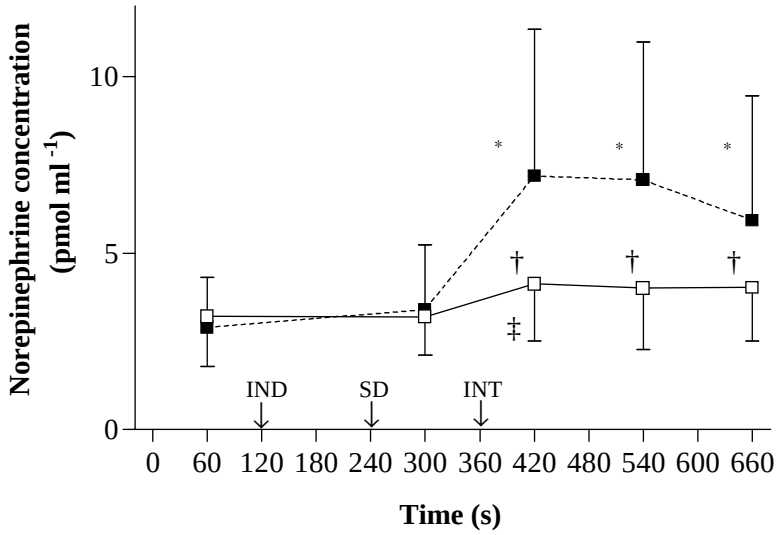

Figure 5 Plasma norepinephrine concentrations during induction of anaesthesia (INT), administration of study drug (SD) and endobronchial intubation (INT) in patients receiving alfentanil (□) or esmolol (■). Values are mean (SD). Norepinephrine concentrations increased after intubation in both groups, but were significantly higher after intubation in the esmolol group (‡$p < 0.05$ between groups). *$p < 0.01$ compared with baseline and pre-intubation; †$p < 0.05$ compared with pre-intubation.

of 185/102 mmHg, and heart rate increased to 102 beat.min^{-1} in a placebo group [1]. In the present study, systolic pressure increased by approximately 35 mmHg to a maximum of 140–150 mmHg in both groups, but remained at or below baseline values. Alfentanil and esmolol attenuate the responses to laryngoscopy and tracheal intubation, and although higher doses have sometimes been used [7, 8, 13], comparable doses have also been effective [6, 12]. Higher doses of alfentanil or esmolol, or a combination [7], might obtund the cardiovascular responses more effectively, although hypotension is more likely [12]. Alternatively, changes in heart rate and arterial pressure might have been less marked had the timing of drug administration been different. After intubation, arterial pressure decreased sooner in the alfentanil group but values were well within the physiological range, and the incidence of hypertension, hypotension and bradycardia requiring escape medication in both groups was low.

It is established that plasma catecholamine concentrations decrease after induction of anaesthesia, but increase significantly after laryngoscopy and tracheal intubation. The increase in norepinephrine concentrations is usually greater than that in epinephrine concentrations. Typically, plasma epinephrine and norepinephrine concentrations of 0.6–1.2 pmol.ml^{-1} and 2.5–4.2 pmol.ml^{-1} 2–3 min after laryngoscopy and tracheal intubation have been reported [9, 11, 16], similar to those in the alfentanil group in our study. Differences between studies may relate to differences in anaesthetic technique, sampling site, sample storage and catecholamine assays, as well as the effects of double-lumen endobronchial rather than tracheal intubation. For example, cardiovascular and catecholamine responses during tracheal intubation [11, 17, 18], bronchoscopy [19] and microlaryngoscopy [20] are less marked when propofol is used for induction of anaesthesia compared with thiopental. The responses are also affected by the duration and force of laryngoscopy [15, 21], and by treatments used, e.g. opioids or beta-blockers [8]. Peak norepinephrine concentrations in this study were approximately 7.2 pmol.ml^{-1} in the esmolol group. Despite using very similar experimental conditions, this value is greater than those in our previous study [1], possibly because the mean dose of thiopental was lower (277.5 mg compared to 327.5 mg). However, the exaggerated increase in plasma catecholamine concentrations after intubation in the esmolol group is consistent with previous data in normotensive [22] or hypertensive [23] patients receiving oral beta-blocking drugs, and in those receiving intravenous beta-blockers at induction of anaesthesia [1, 13, 24]. Magnusson and colleagues [22] found peak norepinephrine concentrations of 7.4 pmol.ml^{-1} during microlaryngoscopy in patients pretreated with metoprolol. Norepinephrine and epinephrine concentrations were greater in the metoprolol group than in control patients, despite arterial pressure and heart rate being lower. Catecholamine concentrations were lower in patients who received fentanyl, alone or in addition to metoprolol. Increased norepinephrine concentrations at rest and in response to exercise have also been demonstrated in patients receiving beta-blockers [25]. Possible explanations for these findings have included decreased norepinephrine clearance in patients receiving beta-blocking drugs [26]. However, alterations in catecholamine kinetics are unlikely after a single dose of esmolol. In contrast to our previous study which included a placebo group, arterial pressure and heart rate were similar in both treatment groups. Increased plasma catecholamines concentrations in the esmolol group are therefore inconsistent with a lack of baroreflex-mediated feedback

inhibition of sympathetic outflow. Esmolol is a β_1-selective adrenergic antagonist which acts upon myocardial β_1 receptors to decrease heart rate and arterial pressure. It has no significant intrinsic sympathomimetic activity, no direct effects on central sympathetic activity, and we are not aware of any effects of beta-blocking drugs on the metabolism or neuronal re-uptake of catecholamines. Increases in plasma epinephrine concentrations in this study were modest, and the increased circulating norepinephrine is likely to have diffused from adrenergic nerve terminals rather than being secreted directly by the adrenal gland. The clinical significance of these findings is uncertain, but suggests exaggerated sympathetic nervous activity in response to a stressful stimulus in patients receiving beta-blockers. In contrast, sympathetic activity in response to a stressful stimulus was attenuated in the alfentanil group, which acts in the CNS. Recent reports have suggested the efficacy of beta-blockade in preventing myocardial ischaemia [27] and reducing cardiac complications in high-risk patients undergoing major surgery [28, 29]. It is not known whether beta-blockade in these circumstances is associated with increased plasma catecholamine concentrations during and after surgery. The possible consequences of increased plasma norepinephrine concentrations include increased systemic vascular resistance, cardiac work and impaired organ perfusion mediated by alpha adrenergic receptors, but the significance of this in different patient groups is unclear. It may be that attenuation of certain end-organ effects by beta-blockade increases the risk of other alpha-mediated adverse effects resulting from increased systemic norepinephrine concentrations, and that decreasing sympathetic nervous system activity by other means is preferable in some patients.

In summary, both alfentanil and esmolol produced similar effects on arterial pressure and heart rate after endobronchial intubation, but plasma norepinephrine concentrations were significantly higher in patients who received esmolol. This supports previous findings that the use of beta-blockers to attenuate cardiovascular responses is associated with increased plasma catecholamine concentrations. We would therefore suggest that other methods to attenuate cardiovascular responses, e.g. opioids, might be preferable in these situations.

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