

Changes in onset time of rocuronium in patients pretreated with ephedrine and esmolol – the role of cardiac output

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Background: We investigated the hypothesis that manipulation of cardiac output (CO) with esmolol (Es) or ephedrine (E) affects the onset time of rocuronium.

Methods: Following anesthesia induction, 33 patients received E (70 µg kg⁻¹), Es (500 µg kg⁻¹) or placebo (P) 30 s before rocuronium (0.6 mg kg⁻¹) administration. Cardiac output was measured non-invasively after intubation every 3 min. The interval from the end of rocuronium administration to the disappearance of all twitches was considered to be the onset time.

Results: Onset time was shorter after E (52.2 ± 16.5 s) and longer after Es (114.3 ± 11.1 s) compared with P (87.4 ± 7.3 s) ($P < 0.0001$). Cardiac output increased ($P < 0.05$) in group E for 15 min after rocuronium. In group Es, CO decreased ($P < 0.05$)

at 3 and 6 min. Cardiac output was higher in group E vs. group Es, 3–6 min post administration of rocuronium ($P = 0.015$).

Conclusion: Pretreatment with E or Es appears to affect the onset time of rocuronium by altering CO as measured with the NICOTM (Non-Invasive Cardiac Output) monitor (Novametric Medical Systems Inc., Willingford, CO).

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MUNOZ et al. found that ephedrine (E; 70 µg kg⁻¹) given 30 s before administration of rocuronium decreased the onset time of rocuronium by 26% (1). This was attributed to an increase in cardiac output (CO) and muscle blood flow, and thus a faster delivery of rocuronium to the neuromuscular junction. Szmuk et al. confirmed these results, finding that the onset time of rocuronium was shorter after administration of E (22%) and longer after esmolol (Es; 26%) as compared with placebo (P) (2). No differences between the treatment groups in heart rate, systolic, diastolic, or mean blood pressure were observed in either study. These findings were explained by a masking effect of the combined hemodynamic responses to Es and E, during use of anesthetic induction agents and laryngoscopy.

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The speed of onset of neuromuscular blockade depends in part on physiological factors such as CO (CO), circulation time and muscle perfusion. Induction agents such as etomidate and ketamine, which maintain CO and blood pressure, have been shown to accelerate the onset of the block and to improve intubating conditions when used in association with rocuronium (3)

In the present study, we investigated the hypothesis that changes in CO (CO) may affect the onset time of rocuronium in patients pretreated with Es or E.

Methods

With approval of the Committee for the Protection of Human Subjects at the University of Texas at Houston and after written informed consent, 33 ASA physical status I–II patients aged 18–60 years were enrolled in this prospective, randomized double-blind study. Patients scheduled for elective general surgery and

gynecologic procedures, and ear, nose and throat procedures under general anesthesia were included. Exclusion criteria included increased risk for aspiration of gastric content (e.g. pregnant, full stomach, or history of regurgitation), anticipated difficult endotracheal intubation (Mallampati class III–IV) and hypertension. Patients were randomly assigned from a computer-generated list to one of three groups of 11 patients each: ephedrine = E, esmolol = Es and placebo = P.

On arrival in the operating room, standard ASA monitors were placed and anesthesia was induced with fentanyl $3 \mu\text{g kg}^{-1}$, propofol 2mg kg^{-1} and succinylcholine 1mg kg^{-1} . Patients were intubated and ventilated using nitrous oxide in oxygen (70/30%) and isoflurane (end-tidal of 1%). Upon recovery of the single twitch response from succinylcholine administration and with the patient in a stable hemodynamic condition (three consecutive BP measurements at 5-min intervals within 20% of the preoperative value), E ($70 \mu\text{g kg}^{-1}$), Es (0.5mg kg^{-1}) or saline placebo was administered. Hemodynamic measurements made immediately prior to study drug administration were defined as baseline. Thirty seconds after the study drug was given, rocuronium (0.6mg kg^{-1}) was administered to all patients. Blood pressure and heart rate were measured and recorded (North American Drager – Narcomed 4, Telfort, PA) every minute for 15 min starting immediately after the administration of rocuronium. During the study period the patient was covered with a warm blanket and no surgical intervention was performed. The anesthesiologist performing induction of anesthesia was blinded as to the study drug used.

Cardiac output was measured using the NICO™ (Non-Invasive Cardiac Output) monitor (Novamatrix Medical Systems Inc., Willingford, CO) after intubation, after recovery of the single twitch response following succinylcholine and before the administration of the study drug, which was defined as baseline, and at 3, 6, 9, 12 and 15 min after rocuronium administration. The NICO™ measures CO every 3 min, so in order to measure the CO as close to the onset of rocuronium as possible, considering a mean onset time of rocuronium of 60 s (4) the study drug was administered 30 s after the baseline CO reading.

Neuromuscular function was assessed with the ulnar nerve at the wrist, using surface electrodes with repeated single twitches for succinylcholine, and train-of-four (TOF) for rocuronium. Supramaximal square wave impulses of 0.2-s duration were administered at 2 Hz every 10 s using a battery-operated stimulator (Constant Current Peripheral

Nerve Stimulator – Fisher & Paykel Health Care NS 252, Auckland, New Zealand). The resulting force of contraction of the adductor pollicis brevis muscle was measured and recorded continuously using a force transducer (Hewlett Packard 78353 A monitor, Boblingen, Germany). Onset time of rocuronium was defined as the time from the end of the administration to the disappearance of all four twitches in the TOF response.

Morphometric and demographic data and the onset times of rocuronium were analyzed using the Chi-square or analysis of variance tests. Student's *t*-tests were applied using Dunnett's correction to compare the onset times of rocuronium between the placebo and other treatment groups. Repeated measurement analysis of variance (ANOVA) was used to identify significant differences in systolic (SBP), diastolic (DBP) and mean blood pressure (MBP), heart rate (HR) and CO. For comparison between groups, we used Bonferroni's correction with an adjusted significance level of 0.017. We also computed the Pearson correlation coefficient to examine the association between CO and the onset time within each group.

Results

The onset time of rocuronium was significantly shorter after E and longer after Es compared with placebo ($P < 0.05$) (Table 1) although the morphometric and demographic characteristics of the patients were similar (Table 1).

There were no differences between the preoperative and baseline blood pressures and the heart rates, and the time for hemodynamic stabilization after induction of anesthesia was 17.3 ± 2.2 min. Systolic blood pressure was significantly decreased in group E at 5, 6, 7, 9, 10, 11 and 12 min ($P < 0.05$) and in group Es from 1 to 5 min ($P < 0.05$). Diastolic blood pressure decreased in group E after 1, 5, 6, 7, 9, 10, 11 and 12 min ($P < 0.05$) and in group Es after 1–5 min ($P < 0.05$). Mean blood pressure decreased in E group after 4–6 min ($P < 0.05$) and in group Es from 1 to 4 min compared with baseline ($P < 0.05$) (Fig. 1). Heart rate decreased in the ES group from 1 to 9 min after administration of rocuronium ($P < 0.05$) compared with the baseline heart rate after induction. The mean blood pressure and heart rate data are presented in Table 2.

CO increased in group E from baseline for 3 to 15 min after rocuronium administration ($P < 0.05$). In the Es group, CO decreased from baseline at 3 and 6 min, respectively ($P < 0.05$) (Table 3). Cardiac output remained higher in group E compared with group Es

Table 1

Morphometric and demographic characteristics of the patients, and onset time of rocuronium.

	Ephedrine (n = 11)	Placebo (n = 11)	Esmolol (n = 11)	P-value
Age (years)	34.6 ± 9.8	34.9 ± 10.3	37.8 ± 13.5	0.767
Gender				
Female	5 (45%)	5 (45%)	6 (55%)	0.886
Male	6 (55%)	6 (55%)	5 (45%)	
Weight (kg)	82.3 ± 12.3	71.5 ± 8.5	81.5 ± 18.7	0.141
Onset time of rocuronium(s)	52 ± 17*	87 ± 7	114 ± 11*	<0.0001

*Significantly different from the placebo group ($P < 0.001$).

at all times 3 to 15 min ($P = 0.015$). No other significant differences in hemodynamic variables were found between the groups. In the placebo group there were no significant differences in CO from baseline.

Pearson correlation coefficients were computed to examine the association between CO and the onset time within each group. While the E group had the highest CO, the onset time of rocuronium was shortest among the three groups. There was a negative correlation between CO and the onset time ($r = -0.243$). The Pearson correlation coefficients between CO and the onset time of rocuronium were 0.441 and 0.204 for the Es and P groups, respectively.

Discussion

We investigated a mechanism that may explain the changes in onset time of rocuronium in patients pretreated with E and Es. Based on the hypothesis that changes in CO are responsible for this effect, we performed non-invasive repeated CO measurements and found a significant increase in CO in the E group compared with the Es group. Cardiac output was increased for 3–15 min after administration of E and decreased 3–6 min after administration of Es. This

finding is consistent with a number of reports on the effect of CO on the onset time of other muscle relaxants. The impact of CO and circulation time is considered by some authors to be greater for faster acting muscle relaxants such as succinylcholine (5) and rocuronium than for intermediate-onset relaxants including mivacurium and vecuronium. Audibert and Donati, for example, showed that reducing muscle blood flow by inflation of a tourniquet produced a delay in the onset time of rocuronium but not of vecuronium and mivacurium (6). Others (7) found that E improved intubating conditions in patients given a low dose of E prior to 0.15 mg kg⁻¹ of cisatracurium, an intermediate-duration non-depolarizing muscle relaxant. This effect is likely related to a quicker onset of neuromuscular block.

When studying onset time, one has to consider the effect of CO on early drug distribution (i.e. front-end kinetics), which determines the plasma drug concentration vs. time relationship seen by the sites of action of a rapidly administered i.v. anesthetic. According to the front-end kinetics phenomenon (8) a decrease in CO actually increases the initial concentrations of the drug, because it is diluted in a smaller volume, and the effect of the drug is likely to be increased. This does not mean that onset is faster. In fact, an increase in CO is likely to accelerate onset only if the drug is given in a high enough dose, which is the case here.

Esmolol, a short-acting, rapid-onset selective beta-1 antagonist, possesses negative inotropic and chronotropic activity, thereby decreasing CO in anesthetized, healthy patients (9). The reduction in CO is dose-dependent, being observed with doses of 100 and 200 mg and with a continuous infusion of Es (9). As expected, the hemodynamic changes were less impressive for the doses used in this study (0.5 mg kg⁻¹). Nonetheless, this dose was sufficient to prolong the onset of rocuronium. Esmolol was found to prolong the recovery from succinylcholine-induced neuromuscular blockade by less than 3 min (10) and to delay the onset of mivacurium in rats (11) and rabbits,

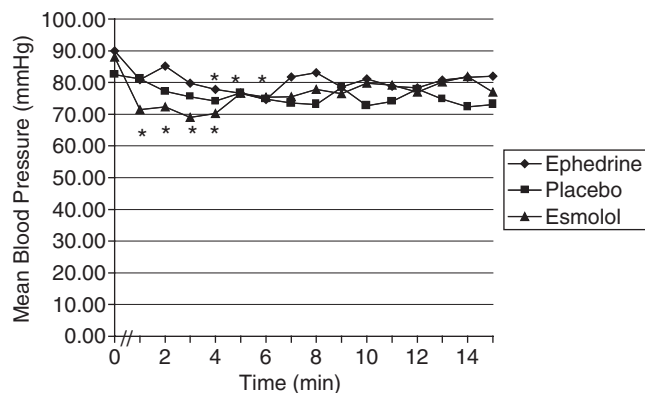


Fig. 1. Mean blood pressure in the three groups. * $P < 0.05$ compared with baseline.

Table 2

Mean arterial pressure and heart rate in the three groups.

Time	Ephedrine		Placebo		Esmolol	
	MAP	HR	MAP	HR	MAP	HR
0	89.9 ± 16.2	87.3 ± 22	82.5 ± 13.7	84 ± 19.9	88 ± 24	90.5 ± 12.6
1	80.9 ± 12.4	82.4 ± 18.6	81 ± 14.2	86 ± 20.1	71.5 ± 9.3*	78.7 ± 7.8
2	85.2 ± 16	82 ± 19.4	77.2 ± 8.5	89.8 ± 20.7	72.4 ± 12.4*	77.5 ± 7.7
3	79.8 ± 17.5	83.1 ± 19.6	75.5 ± 5.6	90.8 ± 17.6	69 ± 14.1*	78.3 ± 8.9
4	77.8 ± 10*	79.6 ± 17.6	74.1 ± 4.6	90.2 ± 17.9	70.3 ± 13.8*	78.4 ± 9.5
5	76.6 ± 6.9*	82 ± 17.9	76.7 ± 7.6	89.3 ± 16.2	76.6 ± 13.8	78 ± 8.8
6	74.6 ± 9.1*	87.6 ± 21	74.7 ± 8.1	90.2 ± 17.5	75.4 ± 15.4	79.1 ± 9.4
7	81.7 ± 10	86.6 ± 22.2	73.5 ± 7.9	85.9 ± 15.6	75.5 ± 13.6	80.2 ± 9.8
8	83 ± 10.1	87.2 ± 23.3	73 ± 9.4	86.1 ± 16.4	77.8 ± 12.8	79.9 ± 9.2
9	78.6 ± 5.6	89 ± 25.1	78.5 ± 12.1	85.3 ± 18.5	76.5 ± 12.8	80 ± 9.1
10	81 ± 7.7	87.2 ± 22.3	72.6 ± 9.9	85.8 ± 18.3	79.7 ± 10.7	81.4 ± 9.5
11	78.8 ± 8.3	83.8 ± 25.2	74 ± 10.3	82 ± 18.8	79.2 ± 11.7	84.5 ± 11.3
12	78.3 ± 9.2	87.4 ± 24.5	78 ± 10.9	82.2 ± 19	76.9 ± 13.7	83.8 ± 12.6
13	80.8 ± 11.3	91.9 ± 22.4	74.7 ± 8.1	83.6 ± 19.4	80.2 ± 12.8	83 ± 11.9
14	81.6 ± 11.1	90.6 ± 25.3	72.3 ± 9.1	83.1 ± 20.8	81.9 ± 11.8	82.1 ± 11.6
15	82 ± 11.4	88.8 ± 23.9	73.1 ± 10.9	84.5 ± 23.4	77 ± 16.4	83.7 ± 11.8

*Significantly different ($P < 0.05$) when compared with baseline.

Numbers are presented as mean and standard deviation in mmHg for the mean arterial pressure and beats per minutes for heart rate. MAP = mean arterial pressure; HR = heart rate; Time 0 = baseline.

where the neuromuscular blocking effect of mivacurium was prolonged by 30% following administration of Es ($100\text{--}500 \mu\text{g kg}^{-1}\cdot\text{min}^{-1}$). This interaction seems to be related to Es-induced decreases in plasma cholinesterase activity.

Ephedrine, a weak, indirect and direct-acting sympathomimetic agent, produces venoconstriction to a greater degree than arterial constriction, causing a redistribution of blood centrally, improving venous return, increasing CO and restoring uterine perfusion. The mild beta action restores HR simultaneously with improvement in venous return. Mild alpha-1-arteriolar constriction does occur, but the overall effect of improved venous return and HR is an increase in CO (12). The effect of E is more marked on systolic than diastolic pressure, thus it maintains organ perfusion by exerting a greater effect on precapillary vascular tone than on venous capacitance (13). Clinical studies have shown that E reaches its peak effect

in 2–5 min and exerts its effect on blood pressure (and probably on CO) in less than 2 min after administration (13).

Effects of E on neuromuscular transmission have also been reported although they occur at concentrations not attainable in clinical practice and can be excluded in the context of this study (14). In order to investigate if E has a direct influence on the neuromuscular junction we computed the correlations within each group and between CO and the onset time of rocuronium within each group. The Pearson correlation coefficient ($r = -0.243$) was the lowest in the E group, suggesting that those with the highest CO have the shortest onset time. Although the correlation was not significant in the other two groups, this may be due to the small number of patients per treatment group, and suggests that a larger study is necessary to examine the effect of drugs at the neuromuscular junction.

Ephedrine was used in association with propofol to improve the hemodynamic stability during induction of anesthesia. Gamlin et al. (13) showed that the addition of 15–20 mg of E to 200 mg of propofol was effective in completely obtunding the hypotensive effect to propofol. Besides causing hypotension, propofol causes bradycardia and addition of E to propofol can help maintain a normal heart rate (13). It is interesting that in awake patients E increased heart rate significantly compared with patients under propofol or sevoflurane anesthesia where the chronotropic effect of E was attenuated (15). The pressor effect of E on

Table 3

Cardiac output (L min^{-1}) in the three groups.

Time	Ephedrine	Esmolol	Placebo
Baseline	6.9 ± 1.3	8.1 ± 2.5	8.2 ± 2.3
3	9.1 ± 1.5*	5.5 ± 1.2*	8 ± 2.3
6	8.9 ± 1.4*	5.7 ± 0.8*	8.4 ± 2.3
9	8.9 ± 1.4*	6.5 ± 0.9	8.5 ± 2.4
12	8.8 ± 1.4*	6.6 ± 1.1	8.2 ± 2.5
15	8.9 ± 1.5*	7 ± 1.3	8.3 ± 2.4

Numbers are presented as mean ± standard deviation.

*Significantly different ($P < 0.05$) when compared with baseline.

patients under propofol or sevoflurane anesthesia seems to be more controversial. At higher doses (15 mg), E significantly increased mean arterial pressure and heart rate (16). At doses similar to those used by us (0.1 mg kg^{-1}), Kanaya et al. (15) found a significant pressure response to E during propofol anesthesia as compared with sevoflurane, whereas Hayakawa-Fujii et al. found that E did not cause any significant pressor response under propofol or isoflurane anesthesia unless patients were pretreated with clonidine (17). The time of maximal effect of E on propofol anesthetized patients was 2–3 min. In our study we found a decrease in mean blood pressure in the E group patients. We administered the study drug after a period of hemodynamic stabilization ($17.3 \pm 2.2 \text{ min}$) and we believe that at this point the hemodynamic effects of propofol and its effects in combination with E were insignificant.

We used succinylcholine for muscle relaxation during induction. Prior administration of succinylcholine in patients was shown to intensify the blocking effect of a subsequent dose of a non-depolarizing blocking drug, such as pancuronium or vecuronium (18). Data on succinylcholine and rocuronium interaction is not available. Nevertheless, we monitored the recovery of the single twitch after administration of succinylcholine for the time of hemodynamic stabilization ($17.3 \pm 2.2 \text{ min}$) and we believe that the effect of succinylcholine on rocuronium was minimal (if any).

Potential of the neuromuscular blockade by volatile anesthetics is a well-known phenomenon. Usually it is not evident on induction and only becomes significant as anesthesia is more prolonged (19). Volatile anesthetics require approximately 45 min to equilibrate between alveolar, blood and muscle compartments (20). The duration of neuromuscular block produced by rocuronium is enhanced, but the time of onset was not affected by sevoflurane and desflurane when compared with isoflurane and propofol (21). Our patients received isoflurane (1%) after induction of anesthesia for $17.3 \pm 2.2 \text{ min}$, which is not sufficient to significantly influence the neuromuscular block of rocuronium.

We, like other authors (1, >2, >7, >20), used TOF as a measure of neuromuscular function. Ideally, the onset time of neuromuscular blocking agents should be measured using a non-conditioned 0.1 Hz single-twitch stimulus pattern (22). A TOF stimulation can be used if the interval between each stimulus is no less than 10 s. Also, it has been shown (23) that the apparent onset time for intermediate-duration neuromuscular blocking drugs, including rocuronium, is faster using a TOF mode of stimulation, mostly because of

the increased muscle blood flow with the higher rates of stimulation.

Currently, thermodilution is the clinical standard for CO measurement although it is invasive and requires the use of a pulmonary artery catheter, which may be associated with morbidity and mortality (24). The main problem in comparing different CO measurement methods is that there is no 'gold' standard for comparison.

The NICOTM monitor measures CO based on changes in the respiratory CO₂ concentration caused by a brief period of rebreathing. Cardiac output measurement is accomplished by interpreting data collected by proprietary sensors that measure flow, airway pressure and CO₂ concentration, then combining these signals to calculate CO₂ elimination. Using these variables, a Fick partial rebreathing technique is applied to calculate CO. The accuracy of the NICOTM monitor has been established in mechanically ventilated surgical patients in the operating room and ICU (25). Bias and precision calculated for the NICO monitor vs. thermodilution collectively averaged $0.12 \pm 0.78 \text{ l min}^{-1}$ for a wide range of patient conditions and clinical practices.

Disadvantages of the NICOTM monitor are that CO can be measured only when a CO₂ trace is available after intubation, and that measurements are intermittent (every 3 min) and rapid changes in CO occurring during the 3-min measuring period may not be appreciated. This problem may occur even with continuous CO measurements. For example, the *in vitro* response time of a change in CO of the IntelliCathTM and Opti-QTM catheters was between 5 and 15 min (26).

We modified our previous protocol (2) so that the 'baseline' time was considered to be the stable interval after the induction of anesthesia and not the preoperative data. This protocol attempted to mitigate the effect of anesthesia induction, laryngoscopy and intubation on the patient's hemodynamics although interactions with isoflurane and succinylcholine cannot be completely excluded, as described earlier.

Our study design has some limitations. First, we measured CO intermittently every 3 min and cannot account for subtle changes occurring during this period. Second, most of the anesthetic and study drugs may have influenced the patients' hemodynamics and the onset time of the neuromuscular blocking agents, thus possibly having a certain effect on our results.

We conclude that the significant reduction (35 s) or prolongation (27 s) of the onset time of rocuronium in patients pretreated with E and Es, respectively, may be due to changes in CO produced by these agents. Further studies with continuous CO and tissue

perfusion measurement is necessary to definitely determine the mechanism of action of E and Es pretreatment on the onset time of rocuronium.

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