The Hemodynamic Effects of Ephedrine on the Onset Time of Rocuronium in Pigs

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Several studies have found a correlation between the onset time of muscle relaxants, cardiac index, and muscle blood flow. Ephedrine increases these hemodynamic variables and shortens onset time of rocuronium in humans. Our aim in this animal study was to determine the effect of ephedrine on the onset time of rocuronium, cardiac index, and muscle blood flow after administration of thiopental. At predefined measuring points, mean arterial blood pressure and cardiac index were measured invasively and onset time was determined mechanomyographically. Twenty-four pigs were randomly assigned to three groups. Group I received etomidate and subsequently rocuronium (2 × 95% effective dose). Instead of etomidate, Group II received thiopental. In Group III, ephedrine 100 μg/kg was given before thiopental; additionally, muscle blood flow was measured (fluorescent microspheres). Although there were differences in hemodynamics between Groups I and II, this was not reflected in different onset times of rocuronium. In Group III, ephedrine compensated the thiopental-induced decrease of mean arterial blood pressure, cardiac index, and muscle blood flow, but no significant shortening of onset time (Group I: 74 ± 21 s; Group II: 71 ± 24; Group III: 69 ± 22 s) was found. Our results demonstrated that ephedrine-related increases in cardiac index and blood flow did not shorten onset time of rocuronium in healthy pigs.

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Several studies have demonstrated that the onset of nondepolarizing neuromuscular blockers may be influenced by either the drug used for induction of anesthesia or the administration of ephedrine or esmolol (1–5). Obviously, the onset time of muscle relaxants is influenced by the hemodynamic changes caused by the anesthetic induction drug also.

In a human study done by Gill and Scott (1), the onset time of vecuronium was significantly shortened after induction with etomidate in comparison to thiopental and propofol. The authors related their findings to the hemodynamic stability of etomidate. Komatsu et al. (6) studied the effect of coadministration of the indirect sympathomimetic drug ephedrine at a dose of 210 μg/kg during induction and found that ephedrine failed to accelerate the onset of neuromuscular block by vecuronium.

In contrast, other authors have found that the coadministration of ephedrine at a dose of 70 μg/kg during induction with thiopental shortened the onset time of rocuronium. These authors attributed this effect of ephedrine to a (partial) compensation of the thiopental-induced diminished cardiac output and muscle blood flow (2,3). Szmuk et al. (4) confirmed the shortening of onset time of rocuronium after coadministration of ephedrine. The proposed mechanism of the influence of hemodynamic variables on onset time remained unproven because these variables were not measured. In a further study by Ezri et al. (5), it was found that pretreatment with ephedrine seemed to affect the onset time of rocuronium by altering cardiac output as measured by a noninvasive method.

The aim of this animal study was to evaluate the effect of treatment with etomidate, or thiopental, and additional administration of ephedrine on onset time of rocuronium. To test the hypothesis that the onset time of rocuronium mainly depends on the hemodynamic profile (arterial blood pressure, cardiac output, and regional muscle blood flow), we measured arterial blood pressure, cardiac output, and peripheral skeletal muscle, larynx, masseter muscle, and diaphragm blood flow with

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fluorescent microspheres and mechanomyographically determined onset time of rocuronium.

Methods

With IRB approval, 24 pigs of both sexes (27 [26–28] kg, median [minimum–maximum]) were anesthetized (azaperone 8 mg/kg body weight [b.w.] IM; piritramide 1.2 mg/kg b.w. IV; and thiopental 5–10 mg/kg b.w. IV followed by an infusion of 12–15 mg/kg b.w./h IV), endotracheally intubated via tracheostomy, and mechanically normoventilated with a fraction of inspired oxygen of 0.3 in air. Catheters were inserted for arterial, pulmonary artery, and central venous pressure monitoring, blood gas analysis, and IV drug administration. In Group III animals, additional catheters were placed in the left cardiac ventricle for microsphere injection and in the intrathoracic aorta for reference blood withdrawal during microsphere injection. Monitoring included electrocardiography, rectal temperature, pulse oximetry, cardiac index (thermodilution method for measuring cardiac output), and continuous display of arterial, central venous and pulmonary arterial pressures, and intermittent blood gas analysis.

Neuromuscular function was assessed by stimulation of the median nerve at the epicondylus medialis humeri using bipolar electrodes with supramaximal single-twitch stimulation at a frequency of 0.1 Hz. The resulting contraction force was measured applying the mechanomyography on the digital superficial flexor muscle and continuously recorded using a force transducer with a neuromuscular function analyzer (Myograph 2000; Biometer Ltd.).

This neuromuscular measuring followed the "good clinical research practice" for pharmacodynamic studies for muscle relaxants as established in the Copenhagen Consensus Conference (7). Neuromuscular measuring was started after the baseline recording of hemodynamic and muscle blood flow. Onset time of rocuronium was defined as the time from the beginning of injection of rocuronium to a 95% reduction of the contraction amplitude. Additionally, the following neuromuscular variables were measured: (a) duration of action, defined as time between beginning of injection of relaxant to recovery of neuromuscular blockade to 25% of baseline values; (b) recovery index, defined as time between 25% and 75% of recovery of neuromuscular blockade; and (c) duration of action, defined as time between beginning of injection of relaxant to recovery of neuromuscular blockade to 90% of baseline values.

Regional muscle blood flow in Group III was determined using fluorescent 15-μm microspheres (Triton Technology Inc.). Two million to 2.5 million spheres per color were injected in a randomized manner into the left ventricle over 30 s. Reference blood was withdrawn from the aortic catheter at a rate of 2 mL/min for 3 min commencing 30 s before microsphere injection. For quantification of the regional blood flow, the fluorescence intensity of the organ probes was set in relation to the fluorescence intensity of the reference blood taking into account the known flow of the reference blood and the weight of the organ probes.

To ensure that the time for reference blood withdrawal was sufficient, a separate blood sample of 1 mL was withdrawn immediately after completion of the 3-min reference blood sampling period, and fluorescence spectroscopy of this sample was performed separately.

The pigs were randomly allocated to 1 of 3 groups: Group I received etomidate and rocuronium (Group I, $n = 8$), Group II received thiopental and rocuronium (Group II, $n = 8$), and a third group additionally received ephedrine (100 μg/kg) before administration of thiopental and rocuronium (Group III, $n = 8$).

For Groups I and II, mean arterial blood and pulmonary artery pressure, heart rate, and cardiac index were measured over a period of 30 s at baseline and 1 min after IV injection of etomidate 0.4 mg/kg thiopental 6 mg/kg, respectively. Directly thereafter, rocuronium 2 × 95% effective dose was injected and, after 1 min, hemodynamic variables were measured. The 95% effective dose of rocuronium in pigs was determined in a pilot experiment to be 1.26 mg/kg.

In the ephedrine group (Group III), hemodynamic variables and, additionally, regional muscle blood flow (larynx, masseter, diaphragm, and peripheral muscle tissue) were determined at baseline and 3 min after administration of IV ephedrine, 100 μg/kg. Directly thereafter, thiopental was injected and, 1 min later, hemodynamic variables and blood flow were measured. Then, rocuronium was injected and measurement was performed after 1 min.

After the experiments, the animals were killed by IV injection of a lethal dose of thiopental and potassium chloride.

Statistical analyses used paired Student's *t*-test and analysis of variance where appropriate. Results are shown as means ± SD; statistical significance was accepted at $P < 0.05$.

Results

The onset time of rocuronium among groups (74 ± 21, 71 ± 24, and 69 ± 22 s in Groups I, II, and III, respectively) revealed no significant difference (Table 1).

However, hemodynamic variables differed significantly: in Group I no changes in hemodynamics were observed during the course of time studied, in Group II the administration of thiopental reduced mean arterial blood pressure and cardiac index, and in Group

Table 1. Onset and Recovery Times

	Group I	Group II	Group III
Onset time (s)	74 ± 21	71 ± 24	69 ± 22
DUR25 (min)	14.07 ± 4.38	13.98 ± 3.02	14.18 ± 3.08
RI (min)	6.1 ± 1.89	4.97 ± 1.19	5.79 ± 1.26
DUR90 (min)	22.07 ± 5.68	21.6 ± 4.93	22.3 ± 4.02

Values are mean ± SD.

Onset time = time from beginning of injection of relaxant to a 95% reduction of the contraction amplitude, DUR25 (duration of action) = time between beginning of injection of relaxant to recovery of neuromuscular blockade to 25% of basic values, RI (recovery index) = time between 25% and 75% of recovery of neuromuscular blockade, DUR90 (duration of action) = time between beginning of injection of relaxant to recovery of neuromuscular blockade to 90% of basic values.

No significant differences among the groups ($P < 0.05$).

III these variables increased after injection of ephedrine. The subsequent administration of thiopental induced a decrease of these variables back to baseline values (Table 2, Fig. 1).

The intergroup comparison showed significantly higher mean arterial blood pressures and cardiac indices in Group I versus Group II and Group III compared with Group II after administration of thiopental (Table 2).

The blood flow in the stimulated muscle increased significantly after stimulation of the median nerve. Injection of ephedrine significantly increased blood flow in all muscles examined. Thiopental induced a significant decrease in blood flow back to baseline values (Fig. 2), respectively back to the value after start of stimulation in the stimulated muscle.

After injection of rocuronium, the blood flow increased slightly, but not significantly. The blood flow in the stimulated muscle decreased significantly almost back to baseline.

Discussion

The onset time of 69–74 seconds obtained was quite short. Other authors found an onset time of 83 seconds in a study with pigs and rocuronium, injected in the right ventricle (7,8). This longer onset time may have been caused by application of a subparalytic dose of rocuronium (0.6 mg/kg).

A comparison of the hemodynamic variables, between Groups I and II, confirmed the well known hemodynamic stability of etomidate in contrast to thiopental. These differences in hemodynamics did not influence the onset time of rocuronium as was also found in a human study by Munoz et al. (9). However, Gill and Scott (1) found a significant shortening of onset time of vecuronium after induction with etomidate compared with thiopental and propofol.

The further results of our animal study confirmed the ephedrine-induced increase in cardiac output and regional muscle blood flow.

The increase of blood flow in the stimulated muscle was attributed to compensation of the increased metabolic demand, which diminished after neuromuscular block by rocuronium. Administration of ephedrine 100 μg/kg before administration of thiopental and rocuronium completely compensated for the hemodynamic depressive effect of thiopental. However, in this animal model, the ephedrine-associated hemodynamic effect failed to improve the onset time of rocuronium, although the ephedrine dose of 100 μg/kg was slightly larger than the ephedrine dose of 70 μg/kg, as used in human studies which found a shortening of onset time of rocuronium (2,4,5).

Our results are consistent with the clinical study of Komatsu et al. (6), in which ephedrine in a relatively large dose of 210 μg/kg also failed to accelerate the onset time of vecuronium.

In contrast, other clinical studies reported that ephedrine shortened the onset time of vecuronium, or rocuronium, respectively, and suggested a close correlation between onset time and cardiac output and muscle blood flow (3–6,10). Iwasaki et al. (11) observed a significant correlation between cardiac index and the onset time of neuromuscular block in patients having cardiothoracic surgery. They found that the speed of onset of paralysis in the adductor pollicis muscle after vecuronium injection into a peripheral vein was clearly related to cardiac output.

In a human study, Audibert and Donati (12) evaluated the influence of circulatory variables on the onset of neuromuscular block after interruption of blood flow to the arm. They found a larger dependency between blood flow and the pharmacologically less potent relaxant rocuronium than for more potent drugs such as vecuronium and mivacurium.

The rate of onset of neuromuscular block depends on the time necessary to build up a pharmacologically effective concentration within the receptor binding regions in the neuromuscular cleft or the so called biophase. This rate, in turn, is influenced by several factors, such as the potency of the drug, the dose administered, and cardiovascular variables such as cardiac output and its distribution and, hence, regional muscle blood flow (12–14).

Previous studies in patients that reported a shortening of onset time after administration of ephedrine were unable to prove a correlation between onset time of rocuronium and cardiac output or regional muscle blood flow, respectively, because these variables were generally not determined or not determined invasively. In addition, the observed changes in heart rate and noninvasively determined arterial blood pressure do not support the hemodynamic hypothesis as the mechanism of action of ephedrine. In the study by Munoz et al. (2), cardiac output and blood flow were not measured and no significant difference was found in heart rate

Table 2. Hemodynamic Variables

	Group I			Group II			Group III			
	Baseline	Etomidate	Rocuronium	Baseline	Thiopental	Rocuronium	Baseline	Ephedrine	Thiopental	Rocuronium
Mean arterial blood pressure (mm Hg)	86 ± 12	87 ± 14	91 ± 16	88 ± 13	46 ± 15*	63 ± 17	81 ± 12	95 ± 18	71 ± 12†	87 ± 14
Heart rate (1/min)	92 ± 16	94 ± 14	97 ± 21	91 ± 14	116 ± 16*	120 ± 18	91 ± 16	94 ± 12	101 ± 14†	99 ± 14
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	4.5 ± 1.4	4.3 ± 1.5	4.8 ± 1.6	4.7 ± 1.4	3.8 ± 1.6*	4.0 ± 1.4	4.4 ± 0.8	5.6 ± 1.2	4.6 ± 1.4†	4.9 ± 0.9
Larynx blood flow (mL/min/100 g)							4.8 ± 0.9	6.3 ± 1.4‡	4.1 ± 1.0§	4.5 ± 0.8
Masseter blood flow (mL/min/100 g)							3.5 ± 0.9	4.5 ± 0.9‡	3.1 ± 0.8§	3.8 ± 0.7
Diaphragma blood flow (mL/min/100 g)							2.1 ± 0.5	3.5 ± 0.7‡	2.3 ± 0.6§	2.6 ± 0.9
Peripheral muscle blood flow (mL/min/100 g)							2.6 ± 0.4	3.7 ± 0.6‡	2.6 ± 0.5§	2.7 ± 0.7

Values are mean ± SD.
* $P < 0.05$ versus Group I etomidate.
† $P < 0.05$ versus Group II thiopental.
‡ $P < 0.05$ versus baseline.
§ $P < 0.05$ versus ephedrine administration.

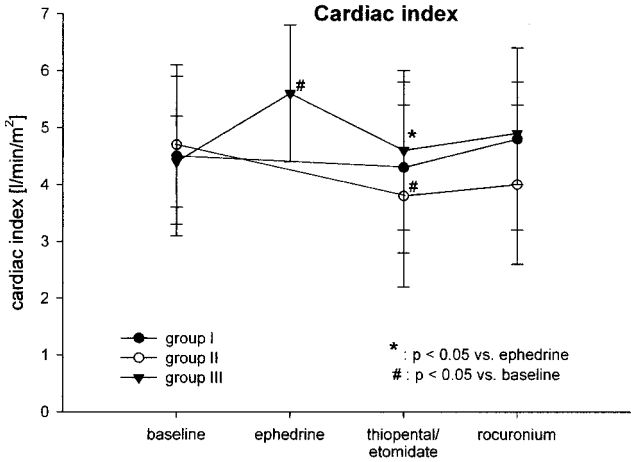

Figure 1. Effect of ephedrine, etomidate, thiopental, and rocuronium on cardiac index. Values are mean ± SD. 1) In Group III significant increase after ephedrine and decrease after thiopental back to baseline values. 2) In Group III significant decrease after thiopental. 3) After thiopental in Group III significantly higher values than in Group II.

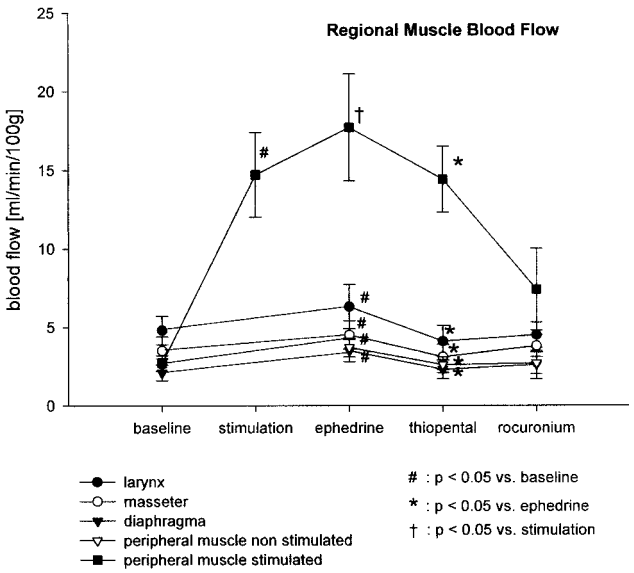

Figure 2. Effect of ephedrine, thiopental, and rocuronium on blood flow in muscles relevant to endotracheal intubation and in peripheral muscles, stimulated and not stimulated. Values are mean ± SD.1) Significant increase after ephedrine and significant decrease after thiopental back to baseline values for all intubation-relevant muscles and nonstimulated peripheral muscle. No change after rocuronium. 2) Significant increase in the peripheral muscle after stimulation. Additional increase after ephedrine and significant decrease after thiopental and rocuronium.

and arterial blood pressure between the group that received ephedrine and the group without. Szmuk et al. (4) did not measure cardiac output in the group of healthy patients. Additionally, the lack of significant heart rate and arterial blood pressure responses after administration of ephedrine leaves a verification of the proposed mechanism open.

In contradiction to Ezri et al. (5), who reported a dependence of onset time of rocuronium from cardiac output, we could not confirm this relation. This difference in findings could be attributed to the different study setup and gives reason for further investigation. Albert et al. (10) confirmed the data of Munoz et al., but they also found no significant hemodynamic effect after induction of anesthesia with or without ephedrine.

Other clinical studies that recorded cardiac indices observed a correlation between onset time and cardiac index only at very low cardiac index values (11).

The results of our study confirmed the known effect of ephedrine on cardiac output and regional muscle blood flow, but did not reveal a significant influence of these hemodynamic changes on the onset time of rocuronium. Because of measurement of cardiac output and muscle blood flow at predefined measuring points, it cannot be excluded that ephedrine was still

maximally effective at the time of injection of thiopental and rocuronium. We presume that in our study the changes of cardiac index after administration of thiopental and ephedrine were small compared with changes of cardiovascular variables in some of the clinical studies cited. Apparently, only substantial variations in cardiac index affect the onset time, and an administration of ephedrine in a dosage of 100 μg/kg does not have a substantial influence on cardiac index if this index is already within a normal range. However, a larger dosage regimen of ephedrine is obviously not indicated in clinical situations because of the possibility of serious adverse effects.

For ethical and practicable reasons, the study had to be performed in anesthetized animals. A background infusion of thiopental was used, according to recommendations for anesthesia in pigs (15). Baseline values for arterial blood pressure and heart rate were comparable to those published for awake pigs (16,17). However, an additional bolus of thiopental caused a significant decrease in cardiac index and blood flow. The same effect could be expected during induction of anesthesia with thiopental in humans.

In this animal model, we were unable to demonstrate that small changes in cardiac output or muscle blood flow that are produced by the different induction drugs, etomidate or thiopental or thiopental plus ephedrine, did not alter the onset of rocuronium. The discrepancies between different studies warrant further elucidation.

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