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## Neuromuscular Effects of Rocuronium on the Diaphragm and Adductor Pollicis Muscles in Anesthetized Patients

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**Background:** Rocuronium has properties that may make it suitable for rapid-sequence intubation. However, its neuromuscular effects have been studied only on the adductor pollicis. This study compares the neuromuscular effect of rocuronium on the diaphragm and adductor pollicis in humans.

**Methods:** The forces generated by the diaphragm and the adductor pollicis during supramaximal single-twitch stimulation of the phrenic and ulnar nerves, respectively, were studied during thiopental, fentanyl, and nitrous oxide-oxygen anesthesia. In 6 patients, cumulative doses of 0.15, 0.25, 0.35, 0.45, and 0.60 mg · kg<sup>-1</sup> rocuronium were given over a 9-min period. The doses for 50% (ED<sub>50</sub>) and 95% (ED<sub>95</sub>) depression of twitch height were calculated. In another 12 patients, the times for maximal effect and 10%, 25%, 50%, 75%, and 90% recovery of the twitch height were calculated after a bolus dose of 0.60 mg · kg<sup>-1</sup> rocuronium.

**Results:** ED<sub>50</sub> and ED<sub>95</sub> were higher for the diaphragm (0.26 ± 0.07 and 0.50 ± 0.20 mg · kg<sup>-1</sup>, respectively) than for the adductor pollicis (0.14 ± 0.05 and 0.24 ± 0.04 mg · kg<sup>-1</sup>). Rocuronium 0.60 mg · kg<sup>-1</sup> produced 100% paralysis of the adductor pollicis in all patients and of the diaphragm in 9 of 12 patients. The onset time for muscle relaxation after 0.6 mg · kg<sup>-1</sup> rocuronium was shorter for the adductor pollicis than for the diaphragm (80 ± 20 vs. 120 ± 62 s). Times for 10%, 25%, 75%, and 90% recovery of twitch height were 34 ± 10, 40 ± 13, 56 ± 20, and 64 ± 21 min, respectively, for the adductor pollicis, and significantly shorter for the diaphragm: 17 ± 10, 23 ± 9, 33 ± 13, and 35 ± 10 min, respectively.

**Conclusions:** The diaphragm is more resistant than the adductor pollicis to rocuronium, as shown by greater ED<sub>50</sub> and ED<sub>95</sub> and faster recovery of the twitch height. The intubating dose of 0.60 mg · kg<sup>-1</sup> is close to the ED<sub>95</sub> of 0.50 mg · kg<sup>-1</sup> for the diaphragm. (Key words: Monitoring: adductor pollicis; diaphragm. Neuromuscular relaxants: rocuronium. Respiratory effects: muscle relaxants.)

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ROCURONIUM is a new steroidal neuromuscular blocking agent characterized by a short onset of paralysis,<sup>1</sup> which makes it particularly suitable for rapid-sequence intubation. The onset of neuromuscular blockade has been established for the adductor pollicis,<sup>1,2</sup> but the neuromuscular effects on respiratory muscles have not. These muscles, including the laryngeal muscles and the diaphragm, are more resistant than peripheral muscles to nondepolarizing relaxants.<sup>3-8</sup>

To demonstrate this relative resistance during the onset of paralysis requires the administration of subparalyzing doses. With this technique, Donati *et al.*<sup>3</sup> found that twice as much pancuronium is necessary to paralyze the diaphragm as is needed to paralyze the adductor pollicis. After a full intubating dose of vecuronium, however, although paralysis of both the diaphragm and the adductor pollicis is complete,<sup>4</sup> the onset time of paralysis is less for the diaphragm than for the adductor pollicis.<sup>4</sup> The faster recovery of the diaphragm with different nondepolarizing relaxants is also explained by its greater resistance compared with that of the adductor pollicis.<sup>4,8</sup>

In the current study, the neuromuscular effects of rocuronium on the diaphragm and the adductor pollicis were compared in anesthetized patients.

### Materials and Methods

The study was approved by the Ethics Committee and written informed consent was obtained from all patients. We studied 18 patients, ASA physical status 1 or 2, undergoing elective surgery for peripheral procedures during general anesthesia. There were 7 men and 11 women aged 44 ± 17 yr and weighing 66 ± 10 kg (mean ± SD). All patients were free of neuromuscular disorders, and none was taking drugs that interfere with neuromuscular transmission. Patients were premedicated with flunitrazepam, 1 mg orally, 2 h before induction of anesthesia with thiopental 6-8 mg · kg<sup>-1</sup> and

fentanyl  $2 \mu\text{g} \cdot \text{kg}^{-1}$ . Tracheal intubation was performed after topical anesthesia with 1–2 ml 2% lidocaine. Ventilation was controlled and adjusted to maintain end-tidal carbon dioxide ( $\text{CO}_2$  Analyzer, Datex, Helsinki, Finland) at 5%. Anesthesia was maintained with 60% nitrous oxide in oxygen using a semiclosed circuit, a fresh gas flow of  $20 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , and additional doses of thiopental, 1–2  $\text{mg} \cdot \text{kg}^{-1}$ . Additional doses of fentanyl, 2–5  $\mu\text{g} \cdot \text{kg}^{-1}$ , were given as necessary.

The ulnar nerve was stimulated (S 88, Grass, Quincy, MA) at the wrist *via* surface electrodes using supramaximal, single-twitch stimulation every 10 s. The developed tension of the adductor pollicis muscle was measured by a force displacement transducer (UC3, Statham). The ulnar nerve was stimulated at least for 5 min before rocuronium was administered. The force of contraction of the diaphragm was estimated from the transdiaphragmatic pressure, defined as the difference between pleural and abdominal pressures and calculated by subtracting gastric pressure from esophageal pressure. These were measured by two thin-walled latex balloons, one placed in the stomach and the other in the middle third of the esophagus after induction of anesthesia. The two balloon catheters were connected to a differential pressure transducer (MP 45, Validyne) accurate to  $\pm 0.5\%$  at  $25 \text{ cmH}_2\text{O}$ . Bilateral phrenic nerve stimulation was performed with Teflon-coated needle electrodes (Dantec, Les Ulis, France), inserted at the inferoposterior border of a sternocleidomastoid muscle. Supramaximal stimulation of the phrenic nerves without propagation to the brachial plexus could be obtained only by transcutaneous stimulation. A single-twitch stimulus with a duration of 0.1 ms was delivered every 10 s. Correct positioning of the balloon was confirmed by observing a negative fluctuation in pressure in the esophageal balloon and a positive fluctuation in the gastric balloon during phrenic nerve stimulation. The stimulus voltage was adjusted to deliver supramaximal stimulation. Maximal stimulation was determined after transdiaphragmatic pressure was stable for 5 min, and the supramaximal voltage was selected at 20 V higher than this voltage required for maximal response (range 70–110 V). The evoked transdiaphragmatic pressure after single-twitch stimulation was approximately  $30 \text{ cmH}_2\text{O}$  (range 20–40  $\text{cmH}_2\text{O}$ ). Phrenic nerve stimulation was performed with the tracheal tube briefly occluded, so that the diaphragm was in its resting position.

In the first part of the study, cumulative dose–response curves were constructed to compare the re-

sponse of the diaphragm with that of the adductor pollicis in 6 patients. Because there may be differences in onset and speed of recovery of rocuronium-induced paralysis between the diaphragm and the adductor pollicis, as there are with other muscle relaxants,<sup>4,8</sup> we standardized the administration times of rocuronium. Because of its short onset of action, rocuronium was administered in cumulative doses of 0.15, 0.25, 0.35, 0.45, and  $0.60 \text{ mg} \cdot \text{kg}^{-1}$ , given at 0, 3, 5, 7, and 9 min, respectively. However, the following dose was given only if a plateau effect (three twitches at the same level) was observed on both the adductor pollicis muscle and the diaphragm. The twitch responses for both muscles were compared with their respective control values to construct cumulative dose–response curves. For each patient, dose–response curves were constructed from the logit transformation of maximum twitch depression *versus* logarithm of the dose, then the effective doses for 50% ( $\text{ED}_{50}$ ) and 95% ( $\text{ED}_{95}$ ) depression of the elicited twitch response were derived from this linear regression analysis for each muscle.

In the second part of the study, a single dose of  $0.60 \text{ mg} \cdot \text{kg}^{-1}$  was administered as a bolus to 12 patients. The following parameters were measured for the two muscles: onset times from the end of injection of muscle relaxant until 50%, 90%, and maximum neuromuscular blockade; the times from injection until recovery of the twitch height to 10%, 25%, 75%, and 90% of control; and the time required for 25–75% recovery of twitch height.

Results are presented as mean  $\pm$  standard deviation. Differences between the parameters measured for the diaphragm and the adductor pollicis were compared by a paired *t* test. Regression lines and correlation coefficients were obtained by the method of least squares. A *P* value less than 0.05 was taken as significant.

## Results

### *Cumulative Dose–Response Relation*

For all patients a plateau effect was obtained for both muscles before the next dose was given. In four of six patients 85–97% blockade of the adductor pollicis was achieved after  $0.25 \text{ mg} \cdot \text{kg}^{-1}$  rocuronium and 100% blockade with the third dose. The dose–response curves for the adductor pollicis and the diaphragm are shown in figure 1. In three of six patients, a complete blockade of diaphragmatic evoked response was not obtained, the maximum blockade in these patients was

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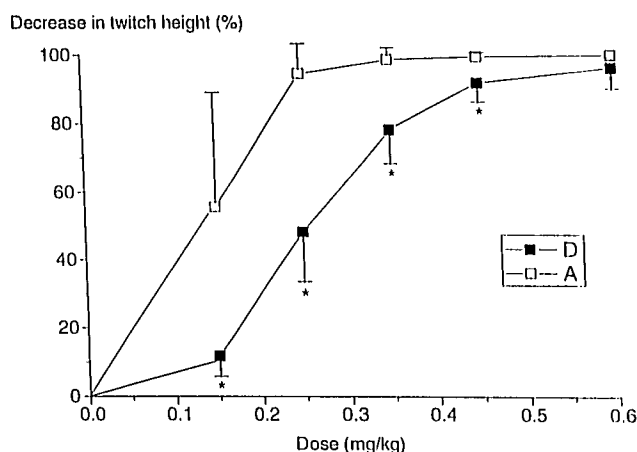


Fig. 1. Cumulative dose-response curves for rocuronium showing percent depression of twitch height (mean  $\pm$  SD) versus dose for the diaphragm (filled symbols) and for the adductor pollicis (open symbols) in six anesthetized patients. \* $P < 0.05$  versus diaphragm.

85%, 96%, and 97% respectively after the cumulative dose of  $0.6 \text{ mg} \cdot \text{kg}^{-1}$ . The dose-response curve of the diaphragm is shifted to the right compared with that of the adductor pollicis. The  $\text{ED}_{50}$  was  $0.14 \pm 0.05 \text{ mg} \cdot \text{kg}^{-1}$  for the adductor pollicis and significantly greater,  $0.26 \pm 0.07 \text{ mg} \cdot \text{kg}^{-1}$ , for the diaphragm ( $P < 0.01$ ) (table 1). The corresponding  $\text{ED}_{95}$  was also significantly greater ( $P < 0.01$ ) for the diaphragm than for the adductor pollicis.

#### Effects of a Single Intubating Dose

The bolus dose of  $0.60 \text{ mg} \cdot \text{kg}^{-1}$  rocuronium induced 100% paralysis of the adductor pollicis in all patients and of the diaphragm in 9 of 12 patients (table 2). In the remaining 3 patients, the maximum depression of the diaphragmatic response was 90%, 95%, and 97% respectively. Onset times from the end of injection of muscle relaxant until 50% and 90% neuromuscular blockade were  $40 \pm 13$  and  $61 \pm 16$  s, respectively, for the adductor pollicis and  $46 \pm 21$  and  $99 \pm 56$  for the diaphragm. The onset time from the end of injection of muscle relaxant until maximum neuromuscular blockade was  $120 \pm 62$  s significantly longer for the diaphragm ( $P < 0.05$ ) than for the adductor pollicis,  $80 \pm 20$  s. Figure 2 illustrates the onset of neuromuscular blocking effect of rocuronium on the adductor pollicis and the diaphragm in 1 of the 12 patients. The diaphragm began to recover from paralysis sooner than did the adductor pollicis (fig. 3): for the diaphragm,

the times required for recovery of twitch height to 10%, 25%, 75%, and 90% of control were less ( $P < 0.001$ ) than for the adductor pollicis. The recovery time was  $8 \pm 4$  min for the diaphragm, less than that for the adductor pollicis,  $17 \pm 9$  min ( $P < 0.01$ ).

## Discussion

### Methodologic Considerations

This study demonstrates important differences in response to rocuronium between the diaphragm and the adductor pollicis. To avoid differences resulting from different methods of measurement, the mechanical response to supramaximal twitch stimulation was analyzed for both muscles. One potential limitation in the assessment of the diaphragmatic response is that its length may change because of decreased functional residual capacity during general anesthesia with the administration of muscle relaxants.<sup>9-11</sup> In this study, anesthetic conditions were similar to those of previous studies on the neuromuscular blocking effect of various agents on the diaphragm,<sup>4,8</sup> in which pleural pressure, measured by esophageal balloon catheter, did not change with the administration of neuromuscular blocking agents, suggesting that functional residual capacity did not change. Furthermore, it has been shown by sonomicrometry that the resting length of the diaphragm is not affected by neuromuscular blockade.<sup>12</sup>

Because the sensitivity to nondepolarizing neuromuscular blocking drugs may vary within the general population, there are inherent limitations in the use of a relatively small sample size to obtain data on dose-response relations and relative onset times of rocuronium at the adductor pollicis and diaphragm.

### Dose-Response Relation

A cumulative dose-response technique has been used to compare the sensitivity of the diaphragm and the adductor pollicis to rocuronium. This method tends to overestimate the effective dose, because when the final

Table 1. Adductor Pollicis and Diaphragm  $\text{ED}_{50}$  and  $\text{ED}_{95}$

	Adductor Pollicis	Diaphragm
$\text{ED}_{50}$ (n = 6)	$0.14 \pm 0.05$	$0.26 \pm 0.07^*$
$\text{ED}_{95}$ (n = 6)	$0.24 \pm 0.04$	$0.50 \pm 0.20^*$

Values are mean  $\pm$ SD (mg/kg).

\*  $P < 0.01$  versus adductor pollicis.

Table 2. Neuromuscular Effect of 0.6 mg/kg Rocuronium on the Diaphragm and the Adductor Pollicis Muscles in 12 Anesthetized Patients

Patient No.	Maximum Effect (%)		OTmx (s)		OT50 (s)		OT90 (s)		T10 (min)		T25 (min)		T75 (min)		T90 (min)		T25-75 (min)			
	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D	A	D		
1	100	100	78	67	35	33	61	48	16	29	19	35	23	44	33	6	4			
2	100	100	75	50	43	25	55	34	27	48	31	61	36	68	38	13	5			
3	100	100	109	134	49	43	66	72	21	47	23	65	36	78	41	18	13			
4	100	100	75	85	41	52	52	71	24	26	13	32	19	35	23	6	6			
5	100	95	92	136	43	41	77	114	28	9	33	14	47	54	25	14	7			
6	100	100	87	184	22	26	54	138	8	23	12	31	17	36	19	8	5			
7	100	100	90	184	56	60	78	168	15	30	20	46	27	56	32	16	7			
8	100	100	48	48	25	29	48	48	23	48	28	73	42	79	46	25	14			
9	100	100	60	105	44	28	41	40	34	55	39	76	44	81	46	21	5			
10	100	100	120	105	68	70	97	100	29	33	16	48	25	ND	28	15	9			
11	100	90	63	204	45	45	54	204	41	0	48	30	65	61	76	31	17			
12	100	97	72	202	32	94	52	152	30	65	35	96	42	102	44	31	7			
Mean ± SD	100	98.5 ± 3.2	80 ± 20	120 ± 62*	40 ± 13	46 ± 21	61 ± 16	99 ± 56	34 ± 10	17 ± 10†	40 ± 13	23 ± 9†	56 ± 20	33 ± 13	64 ± 21	35 ± 10†	17 ± 9	8 ± 4†		

D = diaphragm; A = adductor pollicis; OTmx = onset time of achieving the maximum blockade; OT50 = onset time of achieving 50% of neuromuscular blockade; OT90 = onset time of achieving 90% of neuromuscular blockade; T10, T25, T75, and T90 = time for twitch height recovery to 10, 25, 75, and 90%, respectively, of control value; T25-75 = time from 25% to 75% of recovery of control twitch tension.

\* P < 0.05 versus A.

† P < 0.001 versus A.

dose is given, some of the total dose may already have been eliminated.<sup>13</sup> This phenomenon may be more important for muscle relaxants with intermediate duration of action than for longer lasting agents, because the former are more rapidly cleared from the plasma.<sup>13-15</sup> Although the elimination pathway of rocuronium in humans is not known, it is suggested that rocuronium is as rapidly eliminated from the body as vecuronium<sup>16</sup> and therefore the cumulative technique may underestimate its potency. Bevan *et al.*<sup>17</sup> found that the ED<sub>50</sub> and the dose required for 90% depression of twitch height of rocuronium to be 0.20 and 0.33 mg · kg<sup>-1</sup>, respectively, with the "two-dose" cumulative dose-response method, but that effective doses were greater, 0.21 and 0.42 mg · kg<sup>-1</sup>, respectively, when the single-dose method was used. To minimize this problem in our study, the total cumulative dose was administered over the shortest time possible. Several studies have established the potency of rocuronium in humans.<sup>1,2,17-21</sup> Foldes *et al.*,<sup>1</sup> using the single-dose method, estimated the ED<sub>50</sub> of rocuronium as 0.17 mg · kg<sup>-1</sup>, whereas Bevan *et al.*<sup>17</sup> found it to be 0.21 mg · kg<sup>-1</sup> by the single-dose method and 0.20 mg · kg<sup>-1</sup> by the cumulative method. In our study, rocuronium was found to be slightly more potent, with an ED<sub>50</sub> of 0.14 mg · kg<sup>-1</sup>.

Comparison of the ED<sub>50</sub> and ED<sub>95</sub> for the diaphragm and the adductor pollicis suggests that about twice as much rocuronium is necessary to paralyze the diaphragm. In studies with pancuronium<sup>3</sup> and vecuronium,<sup>4,12</sup> this difference is twofold with pancuronium<sup>3</sup> and only 1.4 times with vecuronium.<sup>5,22</sup> In this respect, rocuronium resembles pancuronium. This diaphragmatic sparing effect of rocuronium is also observed in laryngeal muscles, in which the twitch response is depressed by 77% after a dose of 0.50 mg · kg<sup>-1</sup> of rocuronium.<sup>13</sup> The rocuronium dose required to produce 90% depression of twitch height was found to be 0.68 mg · kg<sup>-1</sup> for the larynx and 0.31 mg · kg<sup>-1</sup> for the adductor pollicis.<sup>23</sup> Although there are differences in the effective dose of rocuronium on the adductor pollicis between our study and that of Meistelman *et al.*,<sup>23</sup> both suggest that there is a high dose-response ratio for rocuronium between respiratory and peripheral muscles.

*Comparative Effects of an Intubating Dose on the Diaphragm and the Adductor Pollicis*

In the second part of the study, the effect of the intubating dose of 0.60 mg · kg<sup>-1</sup> on the two muscles was

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compared. The onset time of muscle relaxation for the adductor pollicis was shorter in our study than in several other studies. This difference may be explained by our methods of monitoring. Recording of the elicited twitch for at least 5 min before rocuronium was administered may have increased local blood flow, which is an important factor influencing the onset time.<sup>24</sup> The onset of full paralysis was shorter on the adductor pollicis than on the diaphragm. However, the onset time to 50% and 90% of neuromuscular blockade was not different for the diaphragm and the adductor pollicis. This contrasts with the findings of a quicker onset of paralysis of the diaphragm with vecuronium, atracurium and succinylcholine using similar conditions.<sup>4,8</sup> Two factors may explain this difference. First, owing to the very short onset time, it may be difficult to demonstrate differences between muscle groups. However, succinylcholine has been shown to paralyze the diaphragm much more rapidly than it does the adductor pollicis.<sup>8</sup> In addition, rocuronium acts more quickly on the vocal cords than on the adductor pollicis<sup>23</sup>; however, the doses of rocuronium were smaller than those used in the current study, resulting in a longer onset time, in excess of 2 min, for the adductor pollicis. Second, the dose-response ratio between the two muscles is particularly high for rocuronium. As a consequence, the dose of  $0.60 \text{ mg} \cdot \text{kg}^{-1}$  given as a bolus or cumulatively, was close to the  $\text{ED}_{95}$  of  $0.50 \text{ mg} \cdot \text{kg}^{-1}$  of the diaphragm, and did not cause complete abolition of the diaphragmatic twitch in 3 out of 12 patients. This may explain why the onset time was longer for

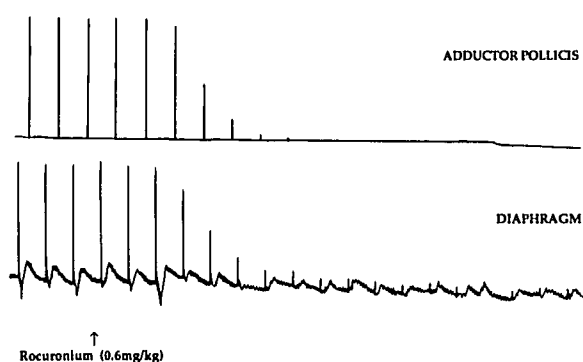


Fig. 2. Simultaneous evolution of the twitch height of the diaphragm and of the adductor pollicis in one patient immediately after the administration of rocuronium (arrow). Supramaximal stimulations of the ulnar nerve and of the phrenic nerves were delivered every 10 s. Oscillations of the baseline of the diaphragm response estimated by the transdiaphragmatic pressure result from the transmission of atrial pressure and from ventilation.

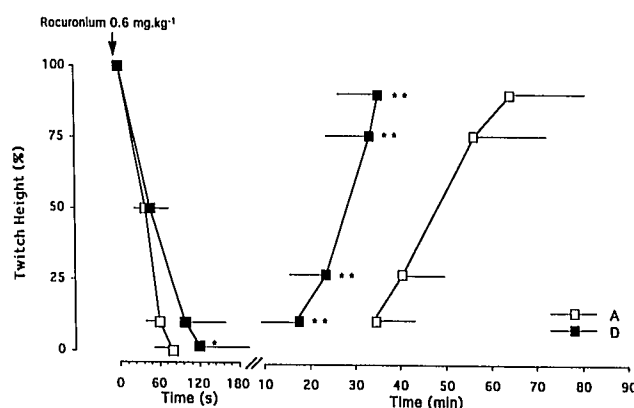


Fig. 3. Evolution of twitch height (mean  $\pm$  SD), expressed as a percentage of the control value, of the diaphragm (filled squares) and the adductor pollicis (open squares) in 12 anesthetized patients after a bolus intravenous dose of  $0.6 \text{ mg} \cdot \text{kg}^{-1}$  rocuronium. \* $P < 0.001$  versus the adductor pollicis.

the diaphragm than for the adductor pollicis. The dose of  $0.60 \text{ mg} \cdot \text{kg}^{-1}$  of rocuronium is less potent at the diaphragm, and even if diaphragmatic blood flow is greater than that of the thumb, a less effective dose of rocuronium will not cause a more rapid effect.

Our results are consistent with those of Meistelman *et al.*,<sup>23</sup> who observed that  $0.50 \text{ mg} \cdot \text{kg}^{-1}$  rocuronium did not produce reliable paralysis of the laryngeal muscles. In addition, Foldes *et al.*<sup>1</sup> observed coughing in 10% of patients after  $0.6 \text{ mg} \cdot \text{kg}^{-1}$  rocuronium, and Wierda *et al.* noted "diaphragmatic coughing" after rocuronium  $0.5 \text{ mg} \cdot \text{kg}^{-1}$ .<sup>25</sup> Hence, we speculate that patients will not always have complete diaphragmatic and vocal cord paralysis after rocuronium  $0.5$ – $0.6 \text{ mg} \cdot \text{kg}^{-1}$  (the proposed recommended dose range for tracheal intubation). Finally, the fast onset of 100% neuromuscular blockade with rocuronium  $0.5$ – $0.6 \text{ mg} \cdot \text{kg}^{-1}$  as measured at the adductor pollicis may not be a good predictor of concurrent optimal intubating conditions.

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