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Differential Sensitivity of Abdominal Muscles and the Diaphragm to Mivacurium

An Electromyographic Study

Krassen Kirov, M.D., Cyrus Motamed, M.D.,* Gilles Dhonneur, M.D., Ph.D.†*

Background: **Respiratory muscles are considered to be more resistant to muscle relaxants as compared with peripheral muscles. However, the relative sensitivity of respiratory muscles participating to the pump function has not been compared. We used electromyography to compare pharmacodynamic parameters of the diaphragm and abdominal muscles after mivacurium.**

Methods: **Forty adults undergoing elective surgery were randomly allocated in five dosing groups of mivacurium (50, 100, 150, 200, and 250 μg/kg). Patients anesthetized with propofol and fentanyl underwent intubation without relaxants. Anesthesia was maintained with nitrous oxide and propofol. The right phrenic nerve, the left 10th intercostal nerve, and the ulnar nerve were stimulated. Electromyography of the diaphragm and abdominal muscles was recorded from surface electrodes. Mechanomyography was used to measure adductor pollicis evoked contraction. After a 5-min stable recording period, patients received a single intravenous bolus (20 s) dose of mivacurium. By using log dose–probit effect regression analysis, dose–response curves were constructed. Effective doses and 95% confidence intervals were derived for the diaphragm and abdominal muscles and were compared.**

Results: **The dose–response regression line of abdominal muscles differed from that of the diaphragm. Calculated ED_{50} and ED_{90} were higher for the diaphragm than for the abdominal muscles (104 [82–127] and 196 [177–213] μg/kg, and 67 [51–82] and 161 [143–181] μg/kg, respectively). The onset of block was faster and recovery of control responses were shorter at the diaphragm than at the abdominal muscles.**

Conclusion: **Diaphragm and abdominal muscles have differential sensitivity to mivacurium. The diaphragm is more resistant to mivacurium than abdominal muscles are.**

RESPIRATORY muscles are considered to be more resistant to neuromuscular blocking agents (NMBAs) than peripheral muscles are. The respiratory sparing effect of muscle relaxants was demonstrated in conscious healthy volunteers breathing spontaneously.[1] Rest ventilation was maintained at a level of block that suppressed peripheral muscle strength.[2] A neuromuscular block causing an almost complete abolition of grip strength also minimally affected maximum inspiratory and expiratory maneuvers.[3] However, during progressive respiratory paralysis, expiratory muscle weakness occurred earlier and for a lower dose of relaxant than inspiratory muscles' fatigue, suggesting a differential sensitivity to muscle relaxants between inspiratory and expiratory muscles.[1–3] In anesthetized patients, the diaphragm was shown to be more resistant to NMBAs than peripheral muscles,[4–6] but few data are available that compare its sensitivity to relaxants with that of other respiratory muscle groups.

To address this issue, we conducted a dose–response study of lateral abdominal muscles and the diaphragm after mivacurium. We choose mivacurium to reduce the likelihood of large variation in pharmacodynamic parameters between subjects. The first dose was selected to approximate what was calculated to be an effective dose causing 50% block at the adductor pollicis.[7] We hypothesized that expiratory abdominal muscles would exhibit an increased sensitivity to mivacurium than that of the diaphragm.

Methods

After institutional ethical approval (Henri Mondor University Hospital, Créteil, France) and with informed consent, we studied 40 adult patients (24 men) with American Society of Anesthesiologists class I or II who were scheduled to undergo elective peripheral orthopedic surgery during general anesthesia. They were between 21 and 53 yr old and had no history of previous abnormal response to neuromuscular agents. All patients were free from renal or hepatic disease and were not taking drugs known to interfere with neuromuscular function.

Anesthetic Management

No premedication was administered. Anesthesia was induced with 3 mg/kg propofol and 2 μg/kg fentanyl, and orotracheal intubation was performed 2 min later without using muscle relaxant. Anesthesia was maintained with 60% nitrous oxide in oxygen and a continuous intravenous infusion of 6–12 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol and was supplemented by bolus doses of 1 mg/kg fentanyl every 30 min. Ventilation was controlled to maintain end-tidal carbon dioxide concentration between 3.5 and 4.5%. During surgery, patients lay supine and were covered with a warm-air heating blanket.

* Staff Anesthesiologist, † Professor in Anesthesia.

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Address correspondence to Dr. Dhonneur: Department of Anesthesiology, Trauma Intensive Care Unit, Henri Mondor University Hospital and Paris XII School of Medicine, Créteil 94 010 Cedex, France. Address electronic mail to: gilles.dhonneur@hmn.ap-hop-paris.fr.

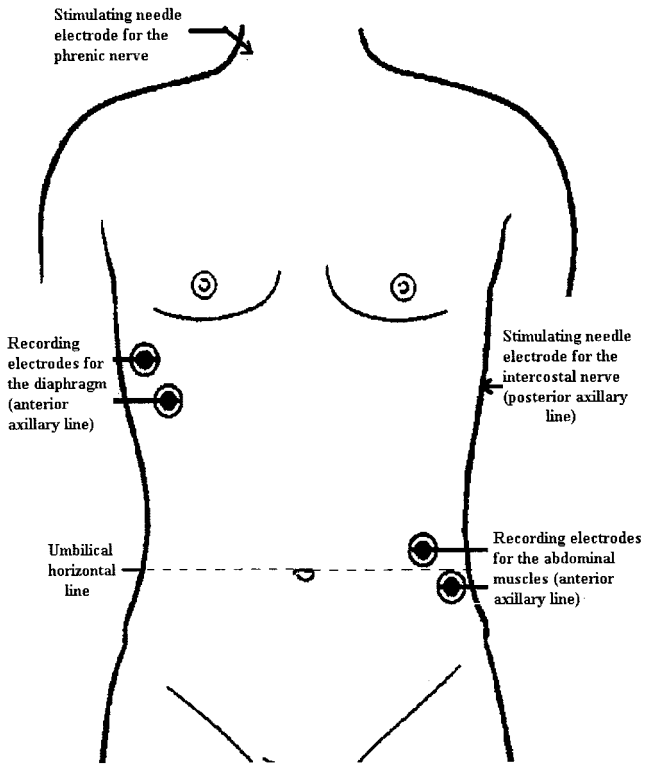

Fig. 1. Electrodes configuration for electromyography of the diaphragm and abdominal muscles.

Measurements

The right phrenic and 10th left intercostal nerves were stimulated using percutaneous insulated needle electrodes inserted at the inferolateral edge of the sternomastoid muscle for the diaphragm and on the posterior axillary line for the abdominal muscles. Satisfactory stimulation of the phrenic and intercostal nerves caused visible hiccuping of the hemidiaphragm and intense reproducible lateral abdominal wall contraction, respectively. Supramaximal single-twitch stimuli (30–45 mA at the right phrenic nerve and 35–55 mA at the 10th intercostal nerve) were applied (0.1 Hz) to both nerves during an end-expiration pause. The resulting evoked activity of the diaphragm (D_{IA}) and abdominal lateral wall (A_{LW}) were measured using silver–silver chloride surface electrodes placed on the anterior axillary line of the thoracoabdominal wall at the seventh or eighth intercostal space (right) and 2 cm apart the horizontal umbilical line (left), respectively (fig. 1). The activity of the muscles was amplified and recorded with a gated electromyographic amplifier using a latency of 2 ms and a window of 20 ms (Viking 2; Nicolet Instruments, Trappes, France). Peak-to-peak amplitude of compound action potential activity of D_{IA} and A_{LW} was measured (fig. 2). The ulnar nerve was stimulated supramaximally at the wrist using train-of-four stimulation every 12 s. The force of contraction of the adductor pollicis (A_p) was measured with a force transducer (Entran, Clayes sous Bois, France).

Clinical Protocol

After steady-state responses for each muscle had been recorded for at least 5 min, the patients were randomly allocated to five dosing groups to receive an intravenous single bolus (20 s) of either 50, 100, 150, 200, or 250 μg/kg mivacurium. The evoked activities of D_{IA} and A_{LW} and A_p were recorded until full recovery. The following parameters obtained from the electromyographic recording and A_p mechanical first response to train-of-four were calculated: maximal effect or depression, times to maximum effect during onset, and recovery of 25, 50, 75 and 90% of initial evoked response. Calculation of recovery indices was relative to end-control.

Statistical Analysis

To evaluate for differences between diaphragmatic and abdominal responses at each dose of mivacurium, the dose–response curve was generated by linear regression of probit of maximal effect or depression on the common logarithm of the dose. The slopes of the regression lines and the derived ED_{50} and ED_{90} values (doses causing 50 and 90% depression of control responses, respectively) for the abdominal muscles and the diaphragm were tested for statistical difference using the Student *t* test. Comparison of pharmacodynamic parameters between D_{IA} and A_{LW} and A_p was performed using a nonparametric Mann–Whitney test. Patient characteristics of each group were compared using analysis of variance. For all statistical comparisons, differences were considered significant when $P < 0.05$.

Results

The mean (SD) age and weight of the patients was 43 (9) yr and 69 (6) kg, respectively. There was no significant difference among the five groups with respect to sex ratio, age, and weight. No adverse events or clinically relevant (exceeding 30% variation of preinduction values) changes in heart rate or blood pressure occurred during the study. Pharmacodynamic parameters of each muscle are presented in tables 1–3. Only the highest dosage of mivacurium (250 μg/kg) caused a 100% depression of the diaphragm and lateral abdominal muscles. The dose–response regression line of the abdominal muscles was significantly ($P < 0.01$) shifted to the left of that of the diaphragm (fig. 3). Mean [confidence interval] ED_{50} and ED_{90} values of abdominal muscles and the diaphragm are presented in table 4. The calculated ED_{50} and ED_{90} of abdominal muscles were smaller ($P < 0.05$) than those of the diaphragm (67 [51–82] and 161 [143–181] μg/kg, and 104 [82–127] and 196 [177–213] μg/kg, respectively). The degree of block attained was more important, and time to attain it was longer ($P < 0.05$) at the abdominal muscles than at the diaphragm. Recovery was faster ($P < 0.05$) at the diaphragm than at the abdominal muscles.

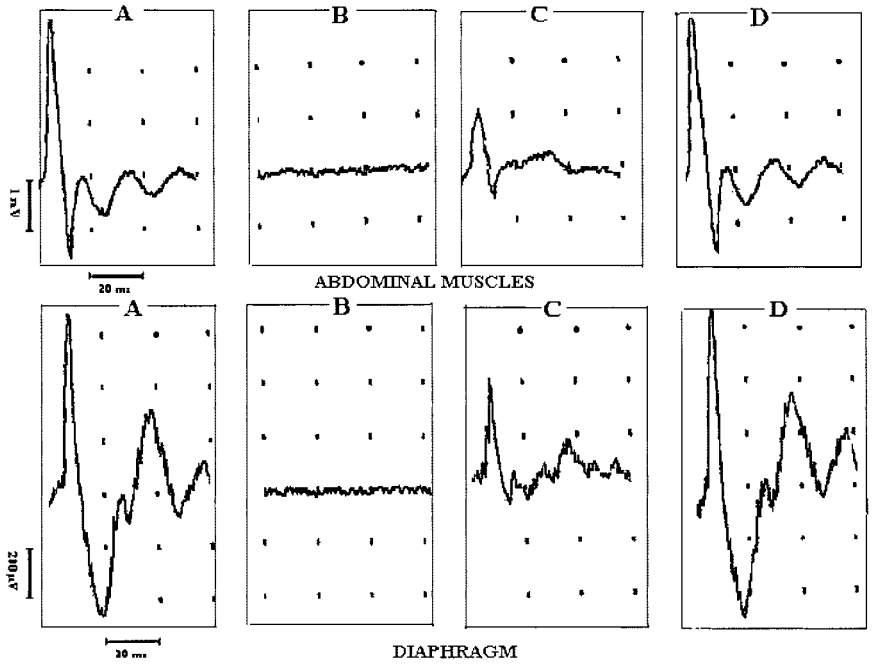

Fig. 2. Typical electromyographic recording after 250 μg/kg mivacurium for the diaphragm and abdominal muscles obtained before (*A*) mivacurium injection, (*B*) maximum effect, (*C*) partial recovery, and (*D*) complete recovery.

Discussion

In the current study, we have demonstrated that abdominal muscles were more sensitive to mivacurium than the diaphragm was. We have observed that both respiratory muscles were more resistant to mivacurium than the adductor pollicis was. The time course of neuromuscular blockade differed significantly between abdominal muscles and the diaphragm.

We used the evoked electromyographic responses to compare the sensitivity of abdominal muscles and the diaphragm to mivacurium because quantification of the mechanical response of these muscles is either impossible or complex and invasive. We are aware that electromyographic assessment of neuromuscular transmission, such as we used, may not indicate the true functional state of the muscle. However, it has been previously demonstrated that NMBAs equally affect the evoked electromyographic activity and the tension developed.[8] It is likely that in the circumstances of the current study, both measurements (electromyography and pressure generation) of the activity of the diaphragm and abdominal muscles would have yielded similar results.

Although surface electromyography to monitor neuromuscular blockade has become a standard for research practice,[9] measurement of the responses of lateral abdominal muscles had not been previously described. Because of unilateral stimulation and the position of the recording electrodes (almost in contact with the muscles studied), we are confident that the method used in the current study allows specific assessment of muscles that constitute the lateral wall of the abdomen. This muscle complex is made of three subcutaneous, superficial, flat muscular sheets (external oblique, internal oblique, and transversus abdominis) supplied by the same nerve roots, which share numerous anatomic and functional characteristics. Because of their fiber orientation, lateral

Table 1. Effect and Time Course of Single-bolus (20 s) Doses of Mivacurium on the Abdominal Muscles

Mivacurium (μg/kg)	T_{MAX} (s)	E_{MAX} (%)	TH_{25} (min)	TH_{50} (min)	TH_{75} (min)	TH_{90} (min)
50	273 ± 49*† [200–330]	40 ± 14*† [12–60]	—	—	—	12 ± 3*† [8–18]
100	210 ± 28*† [180–230]	75 ± 10*† [60–85]	—	10 ± 2*† [7–13]	13 ± 3*† [8–18]	17 ± 3*† [13–22]
150	183 ± 8*† [170–190]	86 ± 9*† [75–97]	10 ± 2*† [6–13]	12 ± 2*† [9–15]	15 ± 3*† [12–19]	19 ± 2*† [17–21]
200	166 ± 19*† [130–180]	94 ± 10*† [78–99]	14 ± 4*† [9–20]	16 ± 4*† [10–23]	18 ± 4*† [12–26]	19 ± 3*† [17–26]
250	145 ± 20* [110–160]	100 —	16 ± 5*† [10–25]	19 ± 5*† [12–28]	22 ± 5*† [19–24]	24 ± 5*† [16–30]

Onset and recovery electromyographic characteristics (mean ± SD, [extreme values]) of the abdominal muscles after mivacurium. Maximal effect (E_{MAX}), time to maximum effect (T_{MAX}), and recovery of 25%, 50%, 75%, and 90% of initial twitch height response (TH_{25}, TH_{50}, TH_{75}, TH_{90}).

* Significantly different from diaphragm. † Significantly different from adductor pollicis.

Table 2. Effect and Time Course of Single-bolus (20 s) Doses of Mivacurium on the Diaphragm

Mivacurium (μg/kg)	T_{MAX} (s)	E_{MAX} (%)	TH_{25} (min)	TH_{50} (min)	TH_{75} (min)	TH_{90} (min)
50	213 ± 29*	24 ± 8*	—	—	—	8 ± 1*
	[180–280]	[10–30]				[7–10]
100	180 ± 25*	52 ± 13*	—	—	10 ± 2*	13 ± 2*
	[170–230]	[32–70]			[7–13]	[11–16]
150	165 ± 23*	78 ± 12*	—	10 ± 2*	12 ± 3*	14 ± 2*
	[120–180]	[60–92]		[7–13]	[6–16]	[12–17]
200	140 ± 22*	85 ± 7*	8 ± 2*	11 ± 2*	13 ± 3*	15 ± 3*
	[100–160]	[75–93]	[5–11]	[7–14]	[8–16]	[10–19]
250	116 ± 22*	100	10 ± 3*	12 ± 4*	14 ± 5*	17 ± 4*
	[90–140]	—	[7–14]	[7–17]	[9–20]	[12–22]

Onset and recovery electromyographic characteristics (mean ± SD, [extreme values]) of the diaphragm after mivacurium. Maximal effect (E_{MAX}), time to maximum effect (T_{MAX}), and recovery of 25%, 50%, 75%, and 90% of initial twitch height response (TH_{25}, TH_{50}, TH_{75}, TH_{90}).

* Significantly different from adductor pollicis.

abdominal muscles act synergistically to compress abdominal content. By this action, the lateral muscle complex was shown to be the most potent expiratory muscle group,[10] particularly efficient at increasing abdominal pressure.[11,12] Moreover, the relative contribution of expiratory muscles to spontaneously breathing anesthetized patients was demonstrated to be mainly due to the recruitment of muscles of the lateral wall of the abdomen.[13–15]

Our results are consistent with those of previous studies that showed a "respiratory sparing" effect of NMBAs. Although statistical challenge focused on comparison between inspiratory and expiratory muscles, we confirm that the dosage of mivacurium required to block abdominal muscles and the diaphragm is higher than that needed to produce a comparable depression of the adductor pollicis tension.[5,16,17] Such increased resistance to relaxant of abdominal muscles as compared with peripheral muscles has been previously mentioned in an experimental setting and suggested by clinical studies.[18–19] Moreover, we have demonstrated that abdominal muscles were more sensitive to mivacurium than the diaphragm was. Our findings reinforce the concept that a relative sparing effect of NMBAs may exist among respiratory muscles. Studies performed in healthy volunteers[1–3] that investigated the effects of progressive paralysis on expiratory and inspiratory muscle strength (assessed by measuring mouth pressure during maximal inspiratory and expiratory efforts against an occluded mouthpiece) foresaw this. The authors observed that at all levels of weakness, expiratory muscle strength was significantly more depressed than was inspiratory muscle strength.[1–3] It was hypothesized that expiratory muscles (intercostal and abdominal muscles) may have a greater sensitivity to NMBAs than the diaphragm does,[1–3] and that their response might be closer to that of the adductor pollicis.[18] We confirm this assumption. Our results suggest that abdominal muscles probably have a lower margin of safety than the diaphragm does.

The results reported currently about the time course of mivacurium-induced neuromuscular blockade at respiratory muscles are similar to those of many previous works. The onset time and duration of action were found to be shorter at both the diaphragm[6,8,9,20,21] and abdominal muscles[19,20] than at the adductor pollicis. Although differences in onset time between lateral abdominal muscles and the adductor pollicis trended to narrow with increasing the dose of mivacurium, the relative brevity of onset of neuromuscular blockade at abdominal muscles is probably a result of their closer

Table 3. Effect and Time Course of Single-bolus (20 s) Doses of Mivacurium on the Adductor Pollicis Muscle

Mivacurium (μg/kg)	T_{MAX} (s)	E_{MAX} (%)	TH_{25} (min)	TH_{50} (min)	TH_{75} (min)	TH_{90} (min)
50	357 ± 47	54 ± 18	—	—	—	14 ± 2
	[300–420]	[13–70]				[13–20]
100	255 ± 30	82 ± 9	14 ± 2	16 ± 2	22 ± 3	25 ± 4
	[220–300]	[70–95]	[11–17]	[13–18]	[17–25]	[20–30]
150	220 ± 22	98 ± 2	16 ± 3	18 ± 3	22 ± 3	26 ± 3
	[190–250]	[94–100]	[12–20]	[14–24]	[18–27]	[22–29]
200	180 ± 22	100	19 ± 3	21 ± 2	25 ± 3	29 ± 2
	[140–200]	—	[16–25]	[20–26]	[22–29]	[26–32]
250	146 ± 21	100	21 ± 3	24 ± 3	26 ± 2	31 ± 3
	[110–170]	—	[18–25]	[21–28]	[24–30]	[28–35]

Onset and recovery of mechanomyographic characteristics (mean ± SD [extreme values]) of the adductor pollicis after mivacurium. Maximal effect (E_{MAX}), time to maximum effect (T_{MAX}), and recovery of 25%, 50%, 75%, and 90% of initial twitch height response (TH_{25}, TH_{50}, TH_{75}, TH_{90}).

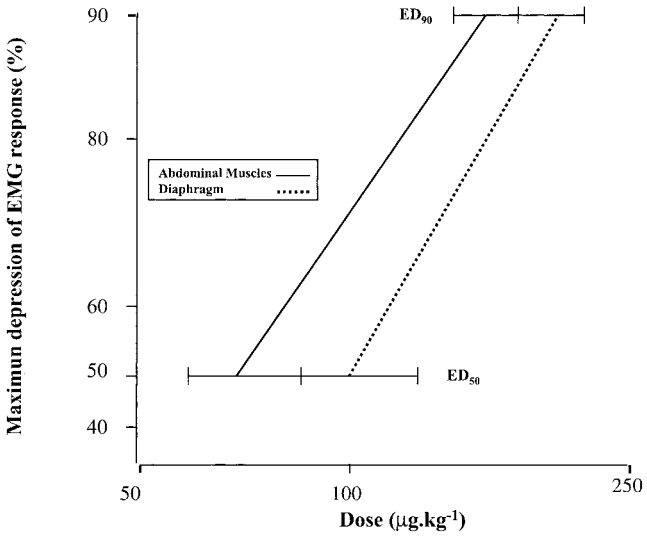

Fig. 3. Dose–response curves for mivacurium showing percent maximum depression of responses to twitch stimuli (probit scale) *versus* dose (log scale) for electromyography (EMG) of the diaphragm and abdominal muscles. The horizontal lines at the ED_{50} and ED_{90} levels indicate 95% confidence intervals.

proximity to the central circulation. However, large differences in onset time between the diaphragm and the abdominal muscles were independent of the dosage, suggesting a shorter transit time of mivacurium at the diaphragm. Differences in arterial muscular blood flow input may explain our observations. Compared with the diaphragm, which is supplied by large arteries directly descending from the aorta, the abdominal muscles are supplied by distal ramification of intercostal arteries.

Because abdominal muscle activity may influence the quality of the surgical procedure, the current results may have several clinical implications for anesthesia daily practice. During induction of anesthesia, the wide discrepancy between the sensitivities of the adductor pollicis and respiratory muscles (diaphragm and abdominal muscles) probably give evidence for the lack of uniformly excellent intubating conditions provided by recommended doses of NMBAs. Intubating recommended dosages of NMBAs are extrapolated from adductor pollicis responses, rather than calculated from respiratory muscle dose–response studies. Our findings reinforce the choice of a fast-onset resistant muscle to monitor both onset of paralysis and depth of surgical relaxation. During abdominal or thoracic open-air surgery in which deep neuromuscular blockade is frequently mandatory, the clinical situation in which abdominal muscle relaxation seems inadequate despite minimal hand muscle response to ulnar nerve stimulation is encountered frequently. This also emphasizes the large dosage of NMBA required to treat both coughing and hiccups when it occurs during anesthesia. In the postoperative period, difference among respiratory muscles in their sensitivity to NMBAs is a powerful argument for systematic reversal of residual neuromuscular blockade. Because ventilation and airway protection are intensely supported by expiratory muscles, oxygenation may be compromised in a patient recovering from anesthesia. During spontaneous ventilation challenge, when expiratory muscles are heavily recruited, residual paralysis may promote fatigue of the abdominal muscles, which was demonstrated to limit ventilation.[22] Partial blockade of abdominal muscles was also shown to alter the efficiency of cough dynamics.[3] The association of depressed airway defense, such as cough reflex, in conjunction with persistent functional impairment of pharyngeal muscles involved in upper airway protective reflexes, such as swallowing,[23] may increase the risk of aspiration. Moreover, long-lasting NMBA-induced residual blockade was demonstrated to be associated with an increased risk of hypoxia in the recovery room and a to be a significant risk factor for development of postoperative pulmonary complications.[24]

Table 4. Effective Doses of Mivacurium

	A_{LW} Electromyography	D_{IA} Electromyography
ED_{50} (μg/kg)	67* [51–82]	104 [82–127]
ED_{90} (μg/kg)	161* [143–181]	196 [177–213]

Calculated effective doses [95% confidence interval] causing 50% (ED_{50}) and 90% (ED_{90}) depression of abdominal muscles (A_{LW}) and the diaphragm (D_{IA}).
* Significantly different from diaphragm.

Conclusion

In summary, we have investigated the concept of "respiratory sparing" of NMBAs. Respiratory muscles are resistant to NMBAs, but a relative sparing exists among respiratory muscles, suggesting a differential resistance to NMBAs between inspiratory and expiratory muscles. The diaphragm is more resistant to mivacurium than abdominal muscles are. If further studies confirm our results, then three categories of muscles' sensitivity to relaxant with important clinical implication may arise during both onset of paralysis and recovery from deep neuromuscular blockade.

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