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Influence of Atracurium on the Diaphragm Mean Action Potential Conduction Velocity in Canines

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Background: **It has been shown that progressive neuromuscular blockade (NMB) affects the electromyogram power spectrum and compound muscle action potential duration in skeletal muscle. These measures are linked to the mean muscle action potential conduction velocity (APCV), but no studies have confirmed a relation between the mean APCV and NMB. The aim of this study was to determine whether diaphragm mean APCV is affected by NMB.**

Methods: **The effects of NMB on diaphragm mean APCV were evaluated in five mongrel dogs. Progressive NMB was induced by slow intravenous infusion of atracurium. During spontaneous breathing, the diaphragm mean APCV was determined by electromyogram signals, in the time and frequency domains. The magnitude of NMB was quantified by the amplitude of the compound muscle action potential and by changes in muscle shortening during supramaximal stimulation of the phrenic nerve.**

Results: **Progressive NMB was associated with a decrease in diaphragm mean APCV. At approximately 70% reduction in the compound muscle action potential amplitude, diaphragm mean APCV had decreased more than 20%. Recovery after NMB was characterized by a restoration of the mean APCV to control values.**

Conclusion: **This study shows that progressive NMB paralyzes motor units within the diaphragm in an orderly manner, and the blockade first affects muscle fibers with high APCV before it affects fibers with lower APCV. (Key words: Diaphragm paralysis; neuromuscular relaxants; sonomicrometry.)**

NEUROMUSCULAR blocking agents interrupt the transmission of nerve impulses to muscle. The sensitivity of different mammalian striated muscle groups to neuromuscular blockade (NMB) varies. Ibebunjo and Hall[1] suggested that muscle sensitivity to both depolarizing and nondepolarizing neuromuscular blocking agents increases with the diameter of the muscle fiber. These authors showed a relation between the 25% recovery time from either vecuronium or suxamethonium block and the fiber diameter, but not with the muscle fiber type (type I *vs.* II). Changes in the sensitivity to NMB within the same muscle also have been observed. Pugh *et al.*[2] found a relative increase in low-frequency power in the electromyogram power spectrum obtained from evoked compound muscle action potentials of the adductor pollicis during atracurium- and vecuronium-induced NMB in humans. Similarly, Harper *et al.*[3] reported that partial NMB with atracurium and vecuronium increased the duration of the evoked compound muscle action potentials in the human adductor pollicis.

The findings of increased low-frequency power in the electromyogram power spectrum[2] and the evidence of increased duration of the evoked compound muscle action potentials[3] imply that NMB may slow the action potential conduction velocity (APCV) in skeletal muscle. Mathematically, the shape of a power spectrum of a moving signal source depends on the velocity of the source, such that the power shifts to higher frequencies if the velocity increases. In this context, it is important to note that APCV refers to 1) single-muscle fiber APCV, 2) motor unit APCV (*i.e.*, the average APCV of all recruited

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single-fiber action potentials that constitute a single motor unit action potential), or 3) the mean APCV of all recruited single-fiber action potentials that constitute the recorded electromyographic signal.

Reports concerning the effect of partial NMB (D-tubocurarine) on single muscle fibers in human and rabbit muscles suggest that NMB does not affect the single-muscle fiber APCV.[4,5] Although NMB has no demonstrated effect on APCV in single muscle fibers, the mean APCV of all muscle fibers can still be subject to an orderly blockade of single muscle fibers with a specific APCV. For example, if muscle fibers with high APCVs are more sensitive to NMB than fibers with low APCVs, progressive NMB would reduce the mean APCV for the entire muscle, whereas the APCV of each fiber would remain unaltered. Considering the fact that the APCV of a skeletal muscle fiber depends on fiber diameter,[6,7] a diameter-dependent orderly blockade of muscle fibers by NMB should reduce the whole muscle mean APCV without altering the single-fiber APCV. Evidence for a relation between NMB and whole muscle mean APCV therefore also would agree with an NMB-induced diameter-dependent orderly blockade of muscle fibers, which was suggested by Ibebunjo and Hall.[1]

Therefore, the study of skeletal muscle mean APCV under NMB may provide 1) additional support for the resistance to vecuronium,[8] rocuronium,[8] and mivacurium[9] of the small fibers in the laryngeal adductor muscles found during clinical anesthesia and 2) some evidence about the order in which different fibers within a muscle are blocked (or unblocked during recovery of NMB).

However, it remains to be determined whether NMB causes a decrease in the mean APCV. The aim of the current study was to determine whether progressive NMB is associated with a decrease in diaphragm mean APCV during spontaneous muscle activity and whether the mean APCV is restored during recovery after NMB.

Materials and Methods

All experiments were performed in the canine diaphragm, because it is one of the skeletal muscles that is resistant to NMB and because it is spontaneously active during anesthesia, which allows electrophysiologic and mechanical parameters to be studied during spontaneous activity and phrenic nerve stimulation. The diaphragm is particularly suitable to measurements of mean APCV during spontaneous activation.[10]

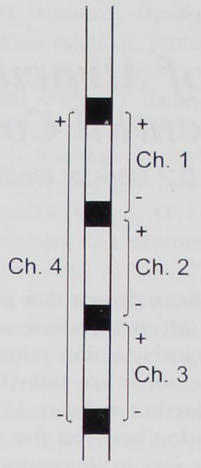

Fig. 1. The bipolar electrode configuration used to obtain the electromyogram. The interelectrode distance was 5 mm for electrode pairs forming channels 1, 2, and 3. The interelectrode distance was 15 mm for the electrode pair forming channel 4.

Instruments

This study was performed in accordance with the Canadian Council on Animal Care guidelines for experiments in animals. The Ethical Committee of the Centre Hospitalier de l'University du Montreal Research Center, Pavillion Notre Dame, University of Montreal, gave its approval. The experiments were performed on five mongrel dogs (average weight, 23 ± 3 kg [SD]) during general anesthesia induced with 30 mg/kg intravenous sodium pentobarbital and maintained with an inhaled mixture of halothane (1%) and oxygen (inspiratory oxygen fraction, 0.7). The trachea was intubated and mechanical ventilation was started. An arterial catheter was inserted in the femoral artery to monitor blood pressure and arterial blood gases. Body temperature was monitored with a rectal probe and kept constant with a heating blanket (at approximately 36 or 37°C).

An electromyographic electrode catheter with four electrode pairs was placed on the abdominal side of the left anterior costal diaphragm *via* a midline laparotomy. Figure 1 shows the electrode arrangement, which consisted of three consecutive channels of 5-mm interelectrode distance (channels 1–3) and one channel of 15-mm interelectrode distance (channel 4). The electrode was aligned in the direction of the muscle fibers and in a region with a low density of motor endplates (typically in the lateral zone of apposition). Regions with low densities of motor endplates were identified using low-voltage stimulation (0.5 V) at 5 Hz, with a stimulus duration of 2 ms. The avoidance of electrode pairs overlying motor end-plates was important to obtain electro-

myographic signals that accurately reflect APCV.[10] Each stainless steel electrode ring was 1.2 mm wide and 1.5 mm in diameter. To ensure that the electrodes remained in position, the electromyographic electrode array was inserted into a tunnel created between the diaphragm and its fascia with a blunt instrument (1.5 mm in diameter) and with no visible disruption of the muscle fibers. To allow for diaphragm shortening, the myofascial tunnel was made 5–10 mm longer than the distance between the tip of the catheter and the most proximal electrode.

In three of the five animals, the diaphragm length was measured with sonomicrometer equipment (Triton Technology, San Diego, CA). Piezoelectric crystals were positioned next to the electromyographic electrode catheter *via* two incisions made 15 mm apart in the fiber direction. At each site, the muscle fibers were separated carefully and a ring of ligature was sutured into the fascia. The elliptically shaped piezoelectric crystals were positioned between the muscle fibers in each penetration zone so they faced each other. The ligature was stretched on the piezoelectric crystals to fix the crystals in place.

Phrenic nerve stimulation was obtained with a bipolar electrode implanted on the left-side phrenic nerve *via* a small neck incision. Spinal anesthesia was used to eliminate sources of cross-talk electromyographic signals from the abdominal and intercostal muscles by paralysis.[11] With the dog lying in the lateral decubitus position in a flexed position with its head and neck elevated, a 22-gauge spinal anesthetic needle was introduced into the lumbar region. When a clear flow of cerebrospinal fluid was obtained from the needle, hyperbaric tetracaine solution (8–10 mg) was injected until all electromyographic activity, recorded with needle electrodes, was eliminated in the parasternal muscles below the third intercostal space. With the head and neck elevated, the animal was turned to the supine position. As determined by the absence of electromyographic activity obtained with a needle electrode in the fourth intercostal space, the spinal anesthesia lasted throughout the entire experiment. Halothane was discontinued and anesthesia was supplemented with intermittent doses of 3 or 4 mg/kg sodium pentobarbital to keep a level of anesthesia that just maintained the corneal reflex.

Signal Acquisition

The four diaphragm electromyographic signals were amplified and bandpass filtered between 16 and 1,600 Hz (model TE4; TECA, White Plains, NY). Electromyographic signals and output from sonomicrometer equipment were A/D converted (DT 2821; Data Translation, Marlborough, MA) with 12-bit accuracy and acquired at 4 kHz onto a personal computer for analysis and storage.

Methods to Determine Diaphragm Mean Action Potential Conduction Velocity

In the current study, determination of the mean APCV was performed only on spontaneous diaphragm electromyographic activity. The diaphragm mean APCV was determined by a frequency-domain–based power spectrum dip technique[10–12] ($APCV_{DIP}$) and a time-domain–based cross-correlation technique[11–13] ($APCV_{XC}$). These methods provide estimates of the mean duration required for multiple motor unit action potentials (activated during a voluntary whole-muscle contraction) to propagate a known distance between electrode rings (dip technique) or between electrode pairs (cross-correlation technique). The dip technique is based on distinct cancellation of power in the electromyographic power spectrum at given frequencies (hence, the so-called dips). These dips occur at frequencies at which the wave length of the electromyographic signal (produced by propagating action potentials) equals one half the interelectrode distance. The mean $APCV_{DIP}$ is determined from the frequency of the first dip and the interelectrode distance. The cross-correlation technique repeatedly compares two signal segments that are obtained from electrodes aligned in the fiber direction while systematically shifting the time base of one signal segment. When the highest correlation between the signal segments is obtained, the time lag between signals can be determined and $APCV_{XC}$ can be calculated because the distance between the electrode pairs is known.

Evaluation of the Level of Neuromuscular Blockade

The phrenic nerve was always stimulated supramaximally (Pekka; Atrostim Inc., Tampere, Finland) with trains-of-five pulses (pulse duration, 0.25 ms) delivered at 10 Hz every 2 s. Peak-to-peak amplitude (V1) of the first of the five compound muscle action potentials elicited by supramaximal stimulation of the phrenic nerve was recorded using the diaphragm electromyogram electrode (channel 4) and was used as an electromyographic index of the level of NMB. In addition, the largest costal diaphragm shortening from resting length (ΔL) observed during the supramaximal stimulation of the phrenic

nerve before the NMB was used as a mechanical index of the level of NMB in three dogs.

Protocol

Approximately 15 min after spinal anesthesia, the animals were evaluated while they breathed spontaneously at rest. The infusion of atracurium (Glaxo-Wellcome, Research Triangle Park, NC) at a rate of 1.5 mg/min was started and continued until spontaneous diaphragm activity was nearly abolished (as determined by the electromyogram and diaphragm shortening). When spontaneous tidal volumes were reduced to about 30% of the control values, the animals were mechanically ventilated (Bird Mark 7, Palm Springs, CA) at a minute ventilation of 6 l/min with a tidal volume of 0.5 l. After the atracurium infusion was discontinued, the animals were allowed to recover until V1 (the peak-to-peak amplitude of the first compound muscle action potential obtained during supramaximal stimulation of the phrenic nerve) was restored to control values (~1 h). Weaning was attempted every 4 or 5 min; when spontaneous ventilation was restored with tidal volumes of approximately 30% of the control values, the ventilatory support was discontinued. After recovery, the same protocol was repeated once. Spontaneous and evoked electromyographic and sonomicrometer signals were acquired approximately every minute during atracurium infusion and every 4 min during recovery. Ten spontaneous breaths and five trains of phrenic nerve stimulation with five pulses at 10 Hz at a rate of 1 train/2 s were acquired in two separate data files.

Statistical Analyses

All statistical methods used were parametric. Group data are presented as mean values with two-tailed 95% confidence intervals ($CI_{95\%}$). The Student's *t* test for paired data was used to compare blood gases before NMB and at the end of the atracurium infusion periods. The effect of different levels of NMB on diaphragm mean APCV was evaluated using one-way analysis of variance for repeated measurements. *Post hoc* multiple comparison was performed using the Tukey test. The strength of the linear association between measures to quantify the level of NMB and diaphragm mean APCV was quantified by calculating the coefficient of correlation for associated variables.

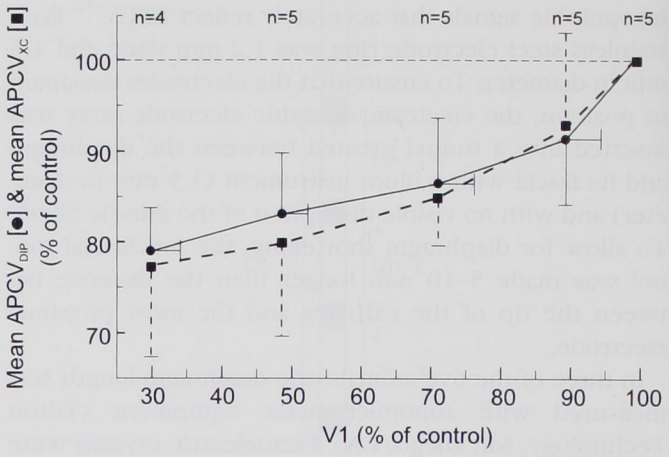

Fig. 2. The relation between the mean diaphragm action potential conduction velocity determined using the dip ($APCV_{DIP}$) and cross-correlation ($APCV_{XC}$) methods during increasing levels of neuromuscular blockade as quantified by changes in the peak-to-peak amplitude (V1) of the first evoked compound muscle action potential. All values are given as the group mean with 95% confidence intervals. The notation "n = #" indicates the number of animals included in the calculation.

Results

The mean blood pressure was 91 ± 14 mmHg ($CI_{95\%}$) and remained stable during the NMB protocol (approximately 2 h). Blood gases obtained during spontaneous breathing and during general anesthesia before NMB were 45.7 ± 4 mmHg ($CI_{95\%}$) for arterial carbon dioxide pressure, and 264.4 ± 126.9 mmHg ($CI_{95\%}$) for the partial pressure of arterial oxygen in the five animals studied. Mean arterial blood *p*H was 7.26 ± 0.07 ($CI_{95\%}$). During NMB (at the end of the atracurium infusion periods and without ventilatory support), the mean arterial carbon dioxide pressure increased 25% (not significant), and *p*H, partial pressure of arterial oxygen, and oxygen saturation decreased by 1, 14, and 4%, respectively (none of the differences was significant).

The control group mean values for diaphragm mean $APCV_{DIP}$ and mean $APCV_{XC}$ before NMB were 3.66 ± 0.59 m/s ($CI_{95\%}$) and 3.52 ± 0.70 m/s ($CI_{95\%}$), respectively. As depicted by the mean values with $CI_{95\%}$ obtained for all animals in figure 2, the current study showed that diaphragm mean $APCV_{DIP}$ and mean $APCV_{XC}$ decreased significantly ($P < 0.05$) during all levels of paralysis except for the V1 at 90% of control with the mean $APCV_{XC}$ technique. High levels of NMB, represented by the 70% reduction in V1, produced more than 20% decreases in $APCV_{DIP}$ and $APCV_{XC}$. Table 1 shows the coefficients of correlation obtained between

Table 1. Correlation between Level of NMB (V1) and Diaphragm Mean APCV Obtained with the Power Spectrum Dip and Time-domain Cross-correlation Methods

Dog Number	NMB and Recovery Period	n	Mean $APCV_{XC}$ *vs.* V1 (r)	Mean $APCV_{DIP}$ *vs.* V1 (r)
1	1	13	0.83	0.79
1	2	11	0.85	0.82
2	1	15	0.87	0.73
2	2	14	0.82	0.62
3	1	21	0.81	0.84
3	2	17	0.69	0.78
4	1	16	0.81	0.67
4	2	14	0.85	0.75
5	1	17	0.78	0.86
5	2	15	0.82	0.81

V1 (expressing the degree of NMB) and diaphragm mean $APCV_{DIP}$ and mean $APCV_{XC}$, respectively, during each infusion period and its subsequent recovery period.

Figure 3 shows the progressive changes in ΔL, V1, and diaphragm mean $APCV_{DIP}$ as a function of time in one dog (dog 3). As depicted in figure 3, infusion of atracurium was associated with reductions in ΔL and V1. Although V1 returned to baseline, ΔL remained substantially below the baseline value obtained before the first infusion of atracurium in two animals (see the upper panel in figure 3). In the third animal in which the diaphragm length was measured, ΔL returned to baseline values after each of the two infusion periods. In the three animals in which the diaphragm length was measured, changes in resting diaphragm length never exceeded 4% at any time during the baseline or infusion periods, suggesting that the functional residual capacity was relatively unaltered. The diaphragm mean $APCV_{DIP}$ decreased and recovered during and after the two infusion periods, respectively (see the third panel in figure 3).

Discussion

Brief Description of Factors that Determine Muscle Fiber Action Potential Conduction Velocity

The conduction velocity of muscle fiber action potentials depends on active and passive components. The passive components (*i.e.*, the cable properties of the fiber) include the capacitance-per-unit length (proportional to the circumference of the fiber) and the internal resistance (inversely proportional to the square of the fiber diameter).[14,15] Theoretical predictions[14] suggest that conduction velocity in fibers with identical membranes should vary as the square root of the fiber diameter. The passive components remain relatively stable during muscle contractions.[12,14,15]

The active components (*i.e.*, the membrane excitability[14,16] expressed through the gating mechanisms of ion channels) depend on ion gradients across the membrane generating the driving electric force, mainly Na^+, K^+, Cl^-, and the properties of the proteins that constitute the gating ion channels. These proteins are influenced by electric field strength, temperature, and the chemical milieu, primarily H^+(*p*H) and Ca^{++} ions.

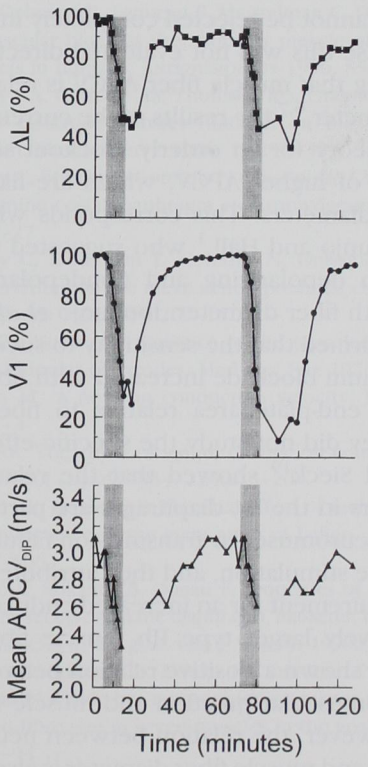

Fig. 3. Two consecutive periods of atracurium infusion (shaded areas) and recovery after neuromuscular blockade in one dog. Changes in peak-to-peak amplitude (V1) of the first evoked compound muscle action potentials, the relative shortening of the costal diaphragm from resting length (ΔL) during the supramaximal stimulation of the phrenic nerve, and the mean diaphragm action potential conduction velocity determined using the dip method ($APCV_{DIP}$) are expressed as a function of time. The segments of missing dip values represent the period of NMB when the animal was receiving ventilatory support.

Possible Mechanism of the Effect of Neuromuscular Blockade on the Mean Action Potential Conduction Velocity

Our results show that the diaphragm mean APCV decreases during progressive NMB. These findings support the view that previous reports of a systematic increase in power in the low-frequency region of the electromyographic power spectrum and increased duration of evoked compound muscle action potentials[2,3] could have been associated with changes in APCV.

As noted before, the possibility that the observed changes in diaphragm mean APCV could be induced by a direct effect of NMB on the muscle fiber is contradicted by the results of previous studies showing that partial NMB with nondepolarizing agents in human and rabbit muscles does not change single-fiber APCV.[4,5] However, the possibility of a direct effect of NMB on single-muscle fiber APCV cannot be rejected completely in the current study, because this was not evaluated directly.

Considering that muscle fiber APCV is related to muscle fiber diameter,[6,7] the results of the current study may support a theory for an orderly blockout starting with single fibers of higher APCV, which are likely to have larger fiber diameters. This corresponds with the findings of Ibebunjo and Hall,[1] who suggested that muscle sensitivity to depolarizing and nondepolarizing drugs increases with fiber diameter. Ibebunjo *et al.*[17,18] subsequently confirmed that the sensitivity to succinylcholine and vecuronium blockade increased with fiber diameter and smaller end-plate area relative to fiber diameter. Although they did not study the specific effect of NMB, Johnson and Sieck[19] showed that the relatively larger type IIb fibers in the rat diaphragm are particularly susceptible to neuromuscular transmission failure after continuous nerve stimulation, and they attributed their findings to a requirement for an increased endplate potential in the relatively larger type IIb muscle fibers. Several reports have shown a positive relation between the size of the neuromuscular junction and muscle fiber diameter.[20–23] However, the relation between neuromuscular junction size and muscle fiber diameter is also influenced by functional properties of the muscle fiber such as muscle fiber type and motoneuron firing rate.[23] In addition, the fiber type itself has been shown to affect the structural properties of the neuromuscular junction, regardless of muscle fiber diameter.[24]

Based on findings of increased variability of the time intervals from two muscle fibers belonging to the same motor unit during partial NMB, or so-called jitter, Ekstedt and Ståhlberg[4] suggested that there is an increase in the synaptic delay between the motor endplates. This finding suggests that also within a motor unit, endplates of different fibers may be differently affected by NMB.

Factors Other than NMB that Can Affect Mean Action Potential Conduction Velocity

As described before, conduction velocity of an action potential depends strongly on the muscle fiber diameter.[6,7] If the area of the muscle fiber membrane is assumed to remain constant, changes in muscle length are expected to affect fiber diameter and, consequently, the single-fiber APCV. However, taking the possible effect of muscle membrane folding into consideration,[25] only very small or no changes in conduction velocity should occur with changes in muscle length.[12,14,15] Controlled experiments *in vitro*[15,26,27] and *in vivo*[12] (using the same method as in the current study to determine diaphragm mean APCV) have not been able to show any significant influence of changes in muscle length (within physiologic limits) on APCV. Changes in temperature influence APCV.[5] In the current study, body temperature showed no changes during the experiment. Increased diaphragm load is another cause of a fatigue-induced reduction in the single-fiber APCV[5] and diaphragm mean APCV.[12,28] However, unless blood pressure decreases, the low force required to obtain an unloaded tidal breath in a dog is not sufficient to cause fatigue[29] or a reduction in diaphragm mean APCV, not even in the presence of spinal anesthesia, paralysis in all intercostal and accessory muscles, increased respiratory drive or acute hypercapnia and respiratory acidosis.[10–12] In the current study, blood pressure remained stable during NMB. Furthermore, the decreases in mean APCV observed during NMB in the current study were more than two times the decrease observed during extreme diaphragm loading.[12] Thus, there is little support that factors other than NMB could explain the more than 20% decrease in the diaphragm mean APCV.

Critique of the Methods

The precision of the methods of diaphragm mean APCV measurement used in the current study are influenced by sampling rate and analysis resolution. In previous studies,[10–12] we estimated the resolution to be approximately 0.1 m/s, which should provide more than sufficient resolution for the current study, considering that the more than 20% decrease in mean APCV corresponds to an absolute value of more than 0.7 m/s. An-

other stochastic influence on the diaphragm mean APCV obtained during voluntary spontaneous breathing is the change in recruitment of motor units with different APCV. The rapid variations of 0.1 to 0.2 m/s of the diaphragm mean $APCV_{DIP}$ seen in figure 3, therefore, can be expected.

The methods used in the current study evaluate diaphragm mean APCV during spontaneous breathing and thus represent a relatively small fraction of all motor units available for recruitment. Therefore, we cannot exclude the possibility that systematic re-recruitment of motor units with different APCV during NMB could produce the changes in diaphragm mean APCV observed. A previous study did not show any systematic changes in diaphragm mean APCV during voluntary breathing with large changes in respiratory drive.[12] These findings contradict the possibility that NMB-induced changes in recruitment produce secondary changes in diaphragm mean APCV.

Cross-talk from muscles located adjacent to the diaphragm is another possible source for systematic influences on electromyogram analysis. This possibility can be ruled out because we have shown before that spinal anesthesia abolishes all cross-talk signals and that the presence of cross-talk signals would hinder the determination of diaphragm mean $APCV_{DIP}$ and mean $APCV_{XC}$.[11]

It should be noted also that the methods used to evaluate V1 and ΔL have a stochastic variability of some magnitude that limits the use of these methods for exact measurements of single events. However, similar to the methods used to determine diaphragm mean APCV, the use of V1 and ΔL to evaluate long-term (over minutes) trends should be suitable for the purposes of the current study.

This study provides evidence that diaphragm mean APCV is affected systematically by the level of NMB. We hypothesized that the decrease in diaphragm mean APCV during NMB is a consequence of an orderly block of muscle fibers in which fibers with high APCV are affected before fibers with low APCV. We also indicated that the APCV-dependent block of muscle fibers is possibly related to the actual diameter of the fibers.

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