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Original Article

Functional Consequences of Eccentric Contractions of the Diaphragm

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ABSTRACT

Introduction and Objectives: Eccentric contractions are those that occur after a muscle has been stretched, and they can predispose the muscle to damage. Most previous studies have been performed on limb muscles, and the potential consequences of eccentric contractions on the respiratory muscles are therefore unknown. The aim of this study was to evaluate the effects of repeated eccentric contractions on diaphragmatic function.
Methods: In 6 dogs, the diaphragm was stretched by applying pressure on the abdominal wall, and consecutive series of eccentric contractions were induced by bilateral supramaximal stimulation. The effect of these contractions on the diaphragm was then evaluated by applying bilateral twitch and tetanic stimulation of the phrenic nerves and measuring the changes in abdominal pressure and the shortening of the right and left hemidiaphragms (by sonomicrometry). Structural study of the muscle was also performed in 4 animals.
Results: Eccentric contractions were successfully achieved in all cases. Stimulation-induced diaphragmatic pressures became lower immediately after these contractions: twitch pressure fell by 53% and tetanic pressure by 67% after the first 10 eccentric contractions (P<.001 in both cases). Tetanic stimulation also demonstrated an early deterioration in contractility, which fell by 29% in the right hemidiaphragm (P<.05) and by 14% in the left hemidiaphragm (P<.001). Functional impairment was persistent, lasting at least 12 hours, and was associated with sarcomeric and sarcolemmal damage.
Conclusions: This experimental model, which enabled the effects of eccentric contractions to be studied in the diaphragm, revealed a deterioration of muscle function that persisted for hours and that appeared to be partly due to structural damage. In the clinical setting, physiologic or therapeutic maneuvers that increase the resting length of the diaphragm should be used with caution.

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Consecuencias de las contracciones excéntricas del diafragma sobre su función

Palabras clave:
Contracciones excéntricas
Diafragma
Lesión muscular

RESUMEN

Introducción y objetivos: Las contracciones excéntricas (CC.EE.) se caracterizan por producirse previa elongación muscular, lo que facilita la lesión. La mayoría de los estudios precedentes se han desarrollado en músculos de las extremidades, por lo que se desconoce la relevancia potencial de las CC.EE. en los músculos respiratorios. El objetivo del presente trabajo ha sido evaluar los efectos funcionales de series repetidas de CC.EE. sobre el diafragma.
Método: Se provocó la elongación del diafragma mediante presión externa abdominal en 6 perros y se indujeron CC.EE. mediante series consecutivas de pulsos supramáximos bilaterales. El efecto se valoró mediante la posterior respuesta del músculo ante estimulación frénica bilateral tanto de pulso único como tetánica, en términos de presión y acortamiento (sonomicrometría) de los hemidiafragmas derecho e izquierdo. En 4 casos se realizó estudio estructural.
Resultados: Se consiguió inducir CC.EE. en todos los casos. Las presiones diafragmáticas inducidas por estimulación disminuyeron inmediatamente después de la actividad excéntrica (pulso único: 53%; tetánica: 67%; $p < 0{,}001$ en ambas, tras las primeras 10 CC.EE.), al igual que la propia contractilidad diafragmática (evidenciable con la estimulación tetánica; hemidiafragma derecho un HD 29%, $p < 0{,}05$, e hemidiafragma izquierdo, un 14%, $p < 0{,}001$). La disfunción fue persistente (duró al menos 12 h) y se asoció a la presencia de daño sarcomérico y sarcolémico.
Conclusión: Con el modelo propuesto, que permite estudiar el efecto de las CC.EE. en el diafragma, se demuestra una pérdida funcional mantenida durante horas, que en parte parece debida a una lesión estructural. Clínicamente se debería ser cauto con las maniobras fisiológicas o terapéuticas que impliquen la elongación basal del diafragma.

Introduction

Contraction of the inspiratory muscles leads to changes in the size and configuration of the thorax, with an increase in the negative pressure within the alveoli and the entry of air into the lungs. The principal respiratory muscle is the diaphragm, which is situated between the thoracic and abdominal cavities and acts as a piston. Its activity can be affected by various factors, including particularly its structural and metabolic integrity and the initial length at which contractile activity begins.[1-3] Contractions that start when the muscle is stretched are called eccentric.[4] These contractions can damage the muscle relatively easily,[5,6] with important functional consequences.[7] However, eccentric contractions appear to be an excellent method for inducing adaptive structural changes in the muscle (remodeling),[8] and some authors therefore recommend their inclusion in rehabilitation programs.[9] The characteristics and consequences of eccentric contractions have been studied in detail in limb muscles.[7] However, the possible consequences on the diaphragm and other respiratory muscles are unknown, probably due to the difficulty involved in designing a suitable in vivo model. Even so, the diaphragm undergoes lengthening of its resting position in a number of situations, such as after implantation of an abdominal wall prosthesis or placement of orthopedic devices that increase intra-abdominal pressure,[10] in patients with ascites or pneumoperitoneum,[11] during certain physiologic maneuvers, rehabilitation exercises and physical training,[12] and with some maneuvers used to measure the maximum respiratory pressures.[13] The objective of this study was to evaluate an animal model for the induction of eccentric contractions of the diaphragm and to determine the functional consequences of these contractions.

Methods

The study was based on elements of a previously validated experimental model.[14] Six mongrel dogs weighing between 20 and 25 kg were anesthetized with 25 mg/kg of intravenous sodium pentobarbital. The animals were then intubated and ventilated mechanically (Mark-8 Respirator, Bird Corporation, Palm Springs, California, USA) and anesthesia was maintained with continuous halothane inhalation. Balloon catheters were then inserted into the esophagus and stomach, and midline laparotomy was performed in order to attach sonomicrometers to the abdominal surface of each hemidiaphragm. The incision was closed by tissue planes and the animals were allowed to recover for 1 week. On the next study day, the animals were reintubated and eccentric contractions of the diaphragm were induced (see below) and their effects on function were evaluated. Finally, euthanasia of the animals was performed with a high intravenous dose of pentobarbital. The structural consequences of the eccentric contractions were evaluated in 4 animals. All the procedures were approved by the ethics committee for animal research of Hôpital Notre-Dame in Montréal.

Induction of Eccentric Contractions

The dogs were placed in the supine position and, after withdrawal of the inhaled anesthesia, they breathed spontaneously through the endotracheal tube. The maintenance dose of pentobarbital was adjusted to keep the muscles physiologically relaxed and the corneal reflex absent.[14] The abdomen was bound tightly by a plaster cast; in the anterior part of the cast, an orifice was made through which a plunger could be used to increase abdominal pressure. After measuring the length of the diaphragm by sonomicrometry, eccentric contractions were induced by electrical stimulation. Stimulation was applied by means of bipolar electrodes that emitted single, bilateral pulses of supramaximal intensity (as explained below). The eccentric contractions were induced in groups, first 10 contractions (given as 5+5), followed by 8, 5, and 5 contractions; each series was separated by at least 10 minutes.

Evaluation of the Effect of Eccentric Contractions

The effect of the eccentric contractions was evaluated after each series by means of bilateral electrical stimulation of the phrenic nerve with 2 modes of induction of the supramaximal response:

single pulse (twitch) stimulation and high frequency (tetanic) stimulation.

Twitch stimulation. This was performed using single bilateral pulses of supramaximal intensity (approximately 8 V, 50 Hz, 0.25 ms).[14] This level was achieved by progressively increasing the stimulus to each nerve from 1 V, until a maximal response was achieved, and then increasing the intensity by an additional 30%. This technique was used both for the induction of eccentric contractions and for the subsequent functional evaluation of their effect. The following experimental conditions were evaluated by twitch stimulation: *a)* baseline, without abdominal binding; *b)* baseline, but after binding with the cast; *c)* immediately after each one of the series of eccentric contractions (short-term effect, with the abdominal cast); and *d)* after completion of all the series and removal of the abdominal cast, at 1, 2, 3, 7, 10, 11, and 12 hours (medium-term effect). At least 2 reproducible maneuvers were performed for each experimental condition.

Tetanic stimulation. This consisted of very high frequency stimulation, which led to fusion of the individual signals. Runs of 50 pulses, resulting in a square-wave pulse, were applied at a frequency of 100 Hz and duration of 0.5 seconds. As in the case of twitch stimulation, at least 2 reproducible maneuvers were performed for each experimental condition. The aim of the tests using tetanic stimulation was to evaluate the short-term effect in greater detail, which meant that these tests were always performed with the abdominal cast in position. The response was evaluated: *a)* before each series of eccentric contractions, and *b)* after each one of these series (the first series was evaluated at 2 timepoints, one after half of the contractions and the second after completing all 10 contractions). At least 2 reproducible maneuvers were performed for each experimental condition.

Muscle response. The muscle response was evaluated by means of the pressures generated and the contractile shortening. The abdominal pressure, indicated by the gastric pressure, was measured using a balloon catheter situated within the stomach. The esophageal pressure was also measured by a second balloon catheter positioned within the esophagus; however, this measurement has not been used in the analysis in the present study because of the frequent induction of artifacts. The catheters were connected to pressure transducers (Validyne MP45-18, Northridge, California, USA). The changes in muscle length (both lengthening and contractile shortening) were evaluated using pairs of piezoelectric crystals positioned on each costal hemidiaphragm. The crystals were connected to a standard sonomicrometry device (Triton Technology Inc, San Diego, California, USA). The physiologic data were recorded on an 8-channel analog polygraph (HP 7758 B, Hewlett-Packard, Palo Alto, California, USA). Results are expressed as the distance between the sonomicrometers in the resting position—length at the baseline functional residual capacity (FRC)—and the percentage of that distance in all other situations.

Muscle damage. We analyzed samples of diaphragm obtained from a subgroup of 4 animals before sacrifice. Sarcomeric damage was determined by electron microscopy, using the procedure published by our group.[2,15] Sarcolemmal discontinuity was evaluated both using standard hematoxylin-eosin staining and by infusion of orange dye before sacrifice, also using the methods previously published by members of the group.[15] Briefly, the presence of the dye within a fiber or intense staining of a fiber with hematoxylin indicates that there are defects in its sarcolemma.

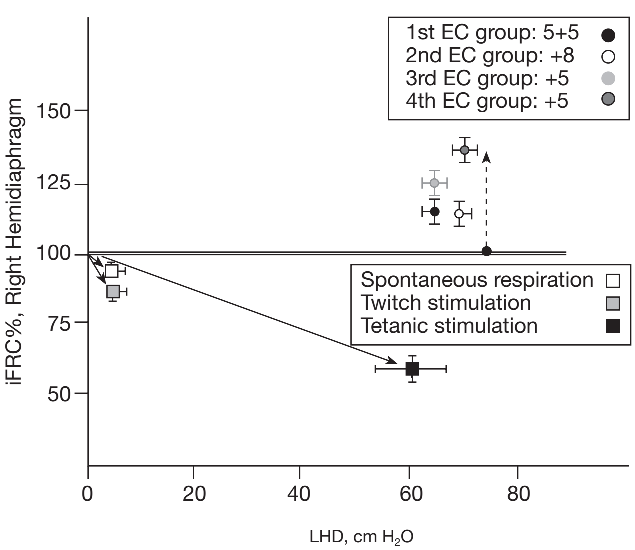

Figure 1. Relationships between the intra-abdominal pressure, represented by the gastric pressure, and the length of the right hemidiaphragm, expressed as the percentage of the length between the 2 sonomicrometers at functional residual capacity at baseline (iFRC%). The mean (SD) values of the intra-abdominal pressures generated experimentally are seen above the iFRC% 100 line (circles, on the right), together with the elongation that this pressure produced in order subsequently to induce the eccentric contractions. The situation is shown for each one of the 4 series performed (different circles). The effect of muscle contraction, both spontaneous and induced by twitch and tetanic stimulation (different oquases) can be seen below the iFRC% 100 line.

Statistical Analysis

All measurements are expressed as the mean (SD). The different conditions were compared by analysis of variance for repeated measures. Significance was established at a *P* value of .05. The structural alterations are only described qualitatively in view of the small number of muscle samples analyzed.

Results

Mechanics of Eccentric Contractions

Using the procedure described, it was possible to induce eccentric contractions in all the animals. Figure 1 shows the intra-abdominal pressure generated in order to achieve the lengths necessary to induce eccentric contractions. These pressures, though relatively high, were very similar to those generated by tetanic stimulation of the diaphragm. The same figure shows the characteristics of the spontaneous muscle contractions and those induced by twitch and tetanic stimulation under basal conditions (concentric contractions), without abdominal binding.

Effect of abdominal binding required to perform eccentric contractions. The mere application of the cast produced a degree of lengthening of the diaphragm (length at FRC, 107% [4%]); this gave rise to greater abdominal pressure in response to stimulation (Figure 2A), despite the moderate decrease in contraction of the left hemidiaphragm.

Effects of Eccentric Contractions on the Response to Twitch Stimulation

Short-term effect (Figure 2A). This evaluation was always performed with the abdominal cast in position, as the time necessary for its removal would have led to a delay in the evaluation of the early response. The successive series of eccentric contractions produced a progressive fall in the pressure generated by the diaphragm after supramaximal stimulation (a fall of 53% after the first series and of up to 73% after the final one). The effects of contractile shortening were small; statistical significance was only reached for a slight and transitory impairment of shortening in the left diaphragm (15%) after a total of 23 eccentric contractions.

Long-term effect (Figure 2B). This evaluation was performed with the diaphragm free (length at FRC, 100%), after removal of the abdominal cast used when performing the eccentric contractions. The pressure generated by the diaphragm in response to twitch pulses was 30% lower and persisted for up to 12 hours after the final

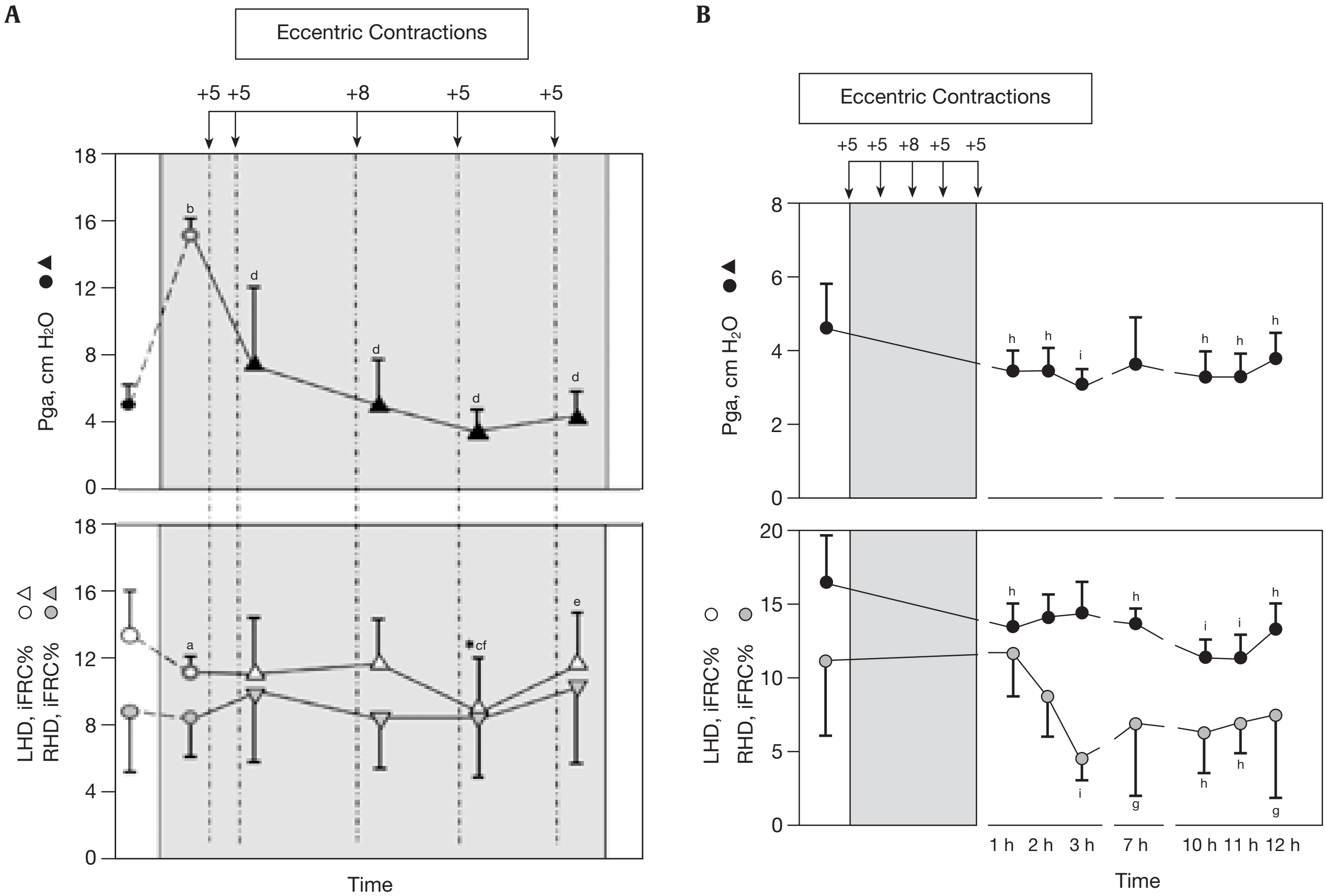

Figure 2. Contractile response of the diaphragm, expressed as the intra-abdominal pressure (gastric pressure), and shortening of the right and left hemidiaphragms after supramaximal twitch stimulation. The shaded area indicates the period when the abdominal cast was in position. *A,* short-term effect of the eccentric contractions after each one of the series (triangles), and *B,* medium-term effect after completing the series and removal of the cast.

[a]*P*<.01 and [b]*P*<.001 for the differences between the 2 basal situations, with (concentric circles) and without (single circles) the abdominal cast.

[c]*P*<.05 and [d]*P*<.001 for the differences between the muscle response to baseline stimulation with the cast and the response immediately after each series of eccentric contractions (triangles).

[e]*P*<.05 and [f]*P*<.01 for the differences between the situation after and immediately before the eccentric contraction.

[g]*P*<.05, [h]*P*<.01 and [i]*P*<.001 for the differences between the muscle response to baseline stimulation without the cast, and the response obtained between 1 and 12 h after completing the series of eccentric contractions and removing the cast.

iFRC indicates initial length of the diaphragm at functional residual capacity; LHD, left hemidiaphragm; Pga, gastric pressure; RHD, right hemidiaphragm.

series of eccentric contractions. The contractions were also weaker, with a fall that occurred slightly earlier in the left diaphragm but that was more marked on the right. Twelve hours after the eccentric contractions had been completed, this change could still be detected (36% in the right hemidiaphragm and 24% on the left).

Effect of Eccentric Contractions on the Response to Tetanic Stimulation

Tetanic stimulation always produced much higher pressures than those achieved during spontaneous breathing or after twitch stimulation. As mentioned above, tetanic stimulation was only used in the detailed analysis of the short-term effect. The abdominal cast was therefore always in position and the diaphragm was slightly lengthened and close to its optimal length. All the series of eccentric contractions produced an immediate fall in the pressure generated by the muscle (a fall of between 67% after the first series and 16% after the final one) and in the intensity of contraction of each hemidiaphragm (falls of between 16% and 36% on the right, and of between 11% and 23% on the left) (Figure 3). It is interesting to note that pressures partially recovered before the following series, about 10 minutes later, although they continued always to be significantly and progressively lower than the baseline value (up to 61% lower before the final series). However, this persistence of effect did not occur with the intensity of the contractile shortening, which returned to baseline values before each one of the series of eccentric contractions.

Muscle Damage

Muscle damage presenting as rupture of continuity of the sarcomeres was found systematically in the muscle samples analyzed, and there were numerous fibers with damaged sarcolemmas (Figures 4 and 5).

Discussion

This study demonstrates that intense eccentric contractions have a damaging and relatively persistent effect on diaphragmatic function, and that this may be related to both structural and metabolic phenomena.

Isotonic muscle contractions (with shortening) can be of 2 types, concentric or eccentric, depending on whether the muscle is initially at its resting length or is stretched. Eccentric contractions of limb muscles can make a muscle lesion more likely to occur[5,6,16] and can have negative

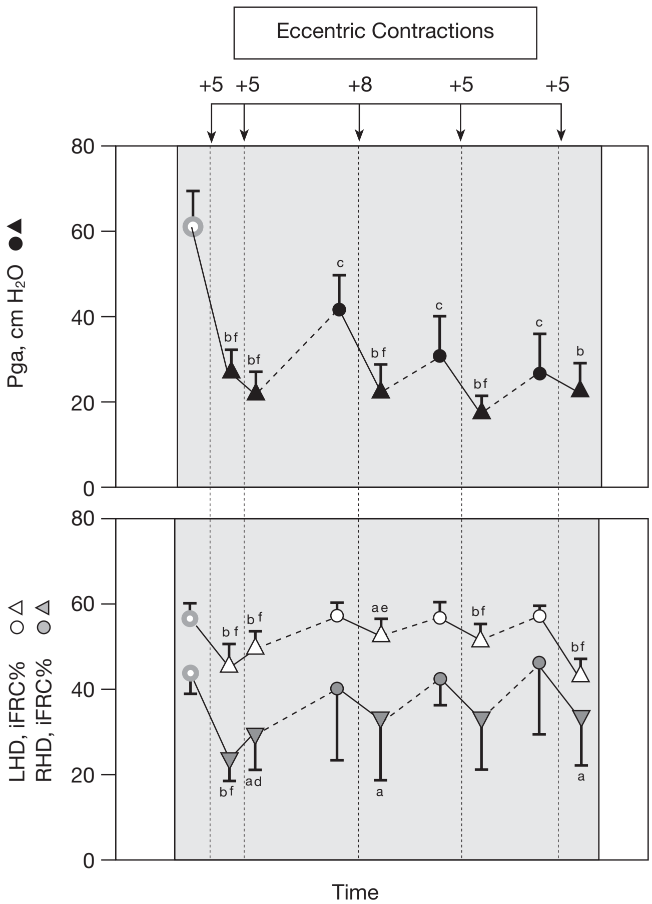

Figure 3. Contractile response of the diaphragm to tetanic stimulation. The shaded area indicates the period when the abdominal cast was in position. The concentric circles represent the baseline situation with the cast in position; the single circles, the situation before a further series of eccentric contractions, after a few minutes' rest, and the triangles, the response after each of these series of contractions.
iFRC indicates initial length of the diaphragm at functional residual capacity; LHD, left hemidiaphragm; Pga, gastric pressure; RHD, right hemidiaphragm.
[a]*P*<.05 and [b]*P*<.001 for the differences between the muscle response to baseline stimulation with the cast and the response immediately after each series of eccentric contractions.
[c]*P*<.001 for the difference between the initial situation and the situation before the series of eccentric contractions.
[d]*P*<.05, [e]*P*<.01 and [f]*P*<.001 for the differences between the response to stimulation before and immediately after each series of eccentric contractions.

effects on contractile function.[7] This study also demonstrated that repeated eccentric contractions of the diaphragm led to an early reduction in the pressure generated by the muscle in response to stimulation. If consecutive series of eccentric contractions occur, there appears to be an additive effect, at least up to a certain number of contractions, after which the pressure does not fall any further. In the initial phase, the fall in contractile efficacy is not usually associated with a lesser degree of shortening, at least after twitch stimulation; this would suggest a loss of continuity in the contractile apparatus. Moreover, persistence of the dysfunction 12 hours after the stimulus supports the hypothesis of the presence of a structural lesion. This could be due to various mechanisms, both mechanical (with opposing force vectors and direct damage to the sarcomeres)[17] and biological (with the induction of oxidative stress, a local inflammatory response, and depletion of glycogen and high-energy phosphates).[15,18-21] An incidental finding of the present study was sarcomeric and sarcolemmal disruption, supporting the implication of some of the aforementioned mechanisms of diaphragmatic dysfunction. Tetanic stimulation enabled us to observe that the immediate harmful effect of the eccentric contractions partially disappeared within a few minutes. This would indicate a mechanism that is not wholly due to structural damage. Some authors believe the early functional change after eccentric contractions may also be due to persistence of elongation or to difficulty realigning the sarcomeres.[22] However, others consider that such dysfunction actually has 2 phases, one early, due to metabolic changes and the other later, linked particularly to a structural problem[23]; the results of the present study would be consistent with that hypothesis. Later, a degree of dysfunction may persist, particularly if muscle regeneration is incomplete, as can occur if the initial lesion is extensive or recurrent or if there are defects in the repair mechanisms. This latter situation appears to develop in the limb muscles of patients with severe chronic obstructive pulmonary disease.[24]

However, eccentric contractions are not necessarily detrimental to a muscle, as they appear to favor adaptive changes more than concentric contractions do, due to a more rapid induction of the expression of transcription factors such as c-Jun and c-Fos,[25] as well as cytokine receptors and ligands,[26] suggesting the early activation of repair programs. In the long term, eccentric contractions appear to generate larger fibers with more sarcomeres,[8,27,28] improving the length-strength relationship[29] and making the muscle more resistant to injury.[30]

With regard to the potential limitations of the study, it should be mentioned that electrical stimulation of the diaphragm can induce esophageal contractions; for this reason, the change of abdominal pressure has been used to evaluate the muscle response, discarding the

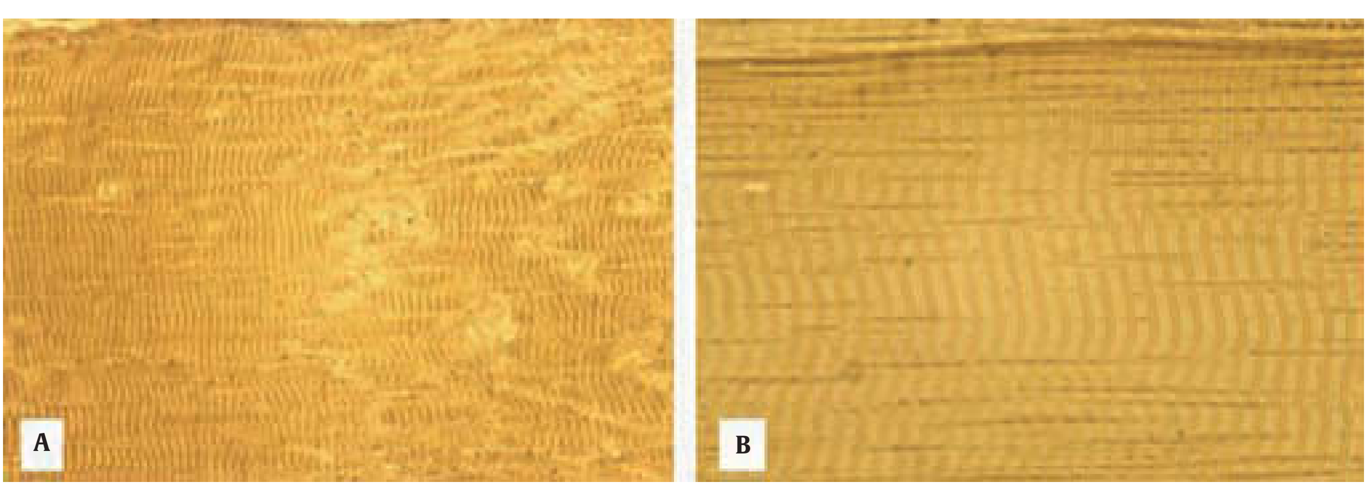

Figure 4. Photograph obtained by electron microscopy (×200, semifine sections set in resin and stained with phenylenediamine) of a sample from the diaphragm of one of the study animals (A) and from a healthy animal (B). In the first, the typical discontinuity of the regular and normal structure of the muscle is seen, characteristic of sarcomeric disruption.

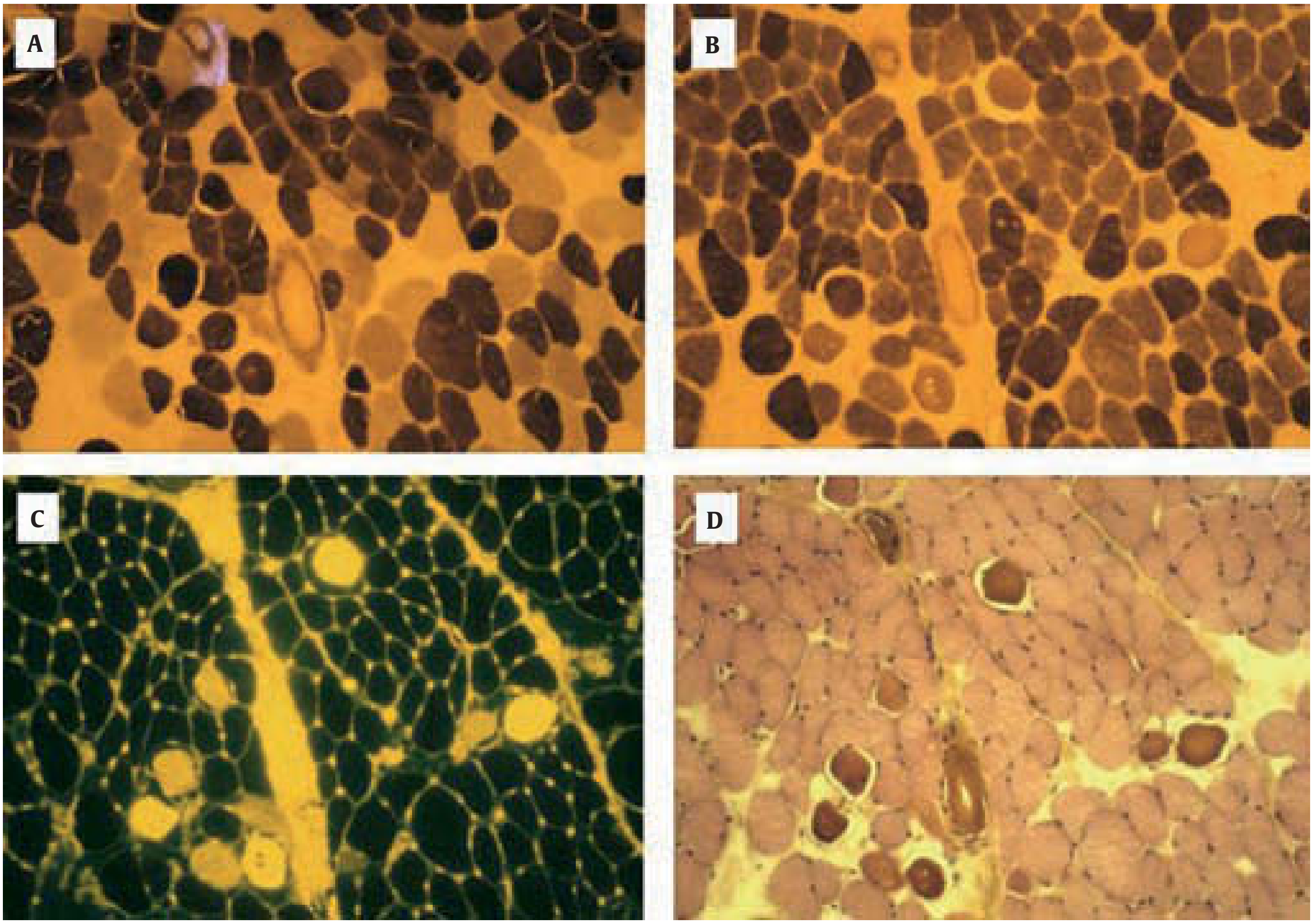

Figure 5. Transverse light microscopy sections corresponding to one of the study animals: A, adenosine triphosphatase (Atlase) stain at pH 4.2, and B, at pH 10.0; C, fluorescence images of the sample stained with orange dye; D, simple hematoxylin-eosin stain. Fibers with a damaged sarcolemma are colored yellow with orange dye and dark brown with hematoxylin-eosin.

esophageal and transdiaphragmatic pressures. Also, a response potentiation phenomenon could have developed, although this is unlikely. The design of the study has minimized this to a reasonable extent, given the number of stimuli in each case and the intervals between each series; in addition, the decrease in the response of the muscle itself would appear to exclude this possibility. Finally, there were no control groups without abdominal casts or with concentric contraction of the diaphragm. With regard to a control group, our research group has recently analyzed the effect of an abdominal cast and found an improvement in contractile strength secondary to changes in the resting length of the muscle[31]; there have also been previous studies that have analyzed the effect of intense concentric contractions,[15,32] whose functional repercussion appears to be much smaller.

The use of abdominal orthopedic corsets is relatively common in clinical practice. Furthermore, the possibility of inducing a more favorable length of the diaphragm has been proposed in order to achieve greater contractile capacity, whether for measurement of maximal pressures[13,33] or for possible clinical benefits. In the clinical context, greater rigidity of the abdominal wall could perhaps partially counteract the detrimental effect of hyperinflation of the lungs by "restretching" the diaphragm. However, it must not be forgotten that this lengthening could also lead to muscle contraction becoming eccentric, with harmful effects. Our study shows that eccentric contractions lead to an impairment of diaphragmatic contractile capacity, and that this still persists 12 hours later, suggesting the presence of structural damage, although it does not exclude a role for other factors. However, there are at least 2 reasons for believing that the eccentric contractions that occur under physiologic conditions do not have such significant negative consequences. First, the series of contractions induced in the present study constitute an extreme situation on account of their intensity and this would be difficult to match in clinical practice. Second, as eccentric contractions also favor a change of muscle phenotype, they could even have a beneficial effect in the long term by contributing to diaphragmatic remodeling. In fact, we know that this muscle is easily damaged in patients with chronic obstructive pulmonary disease,[2] but that a favorably modified phenotype has also been observed.[3]

In conclusion, eccentric contractions can produce functional impairment of the diaphragm. The earliest changes are probably due in part to metabolic disturbances, whereas the later ones are caused by structural lesions.

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