Laryngeal Response to Hypoxia in Awake Lambs during the First Postnatal Days

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ABSTRACT

We recently showed that hypoxia does not induce active expiratory glottic adduction in awake lambs more than 10 d old. To reconcile our results with previous data from other researchers, we hypothesized that an active expiratory glottic closure might still be part of the response to hypoxia in the very first postnatal days. The present study was undertaken to test this hypothesis. We studied 22 awake, nonsedated lambs during hypocapnic hypoxia (fraction of inspired $O_2 = 0.08$ during 15 min) induced during the first 72 h of postnatal life. We recorded airflow via a facial mask and pneumotachograph, along with the electromyographic activity (EMG) of the thyroarytenoid muscle (a glottic adductor) in 10 lambs. We also recorded the EMG of both the posterior cricoarytenoid ($n = 4$) and cricothyroid ($n = 5$) muscles (glottic abductors), as well as the abdominal muscles ($n = 4$). We identified typical expiratory airflow braking on the breath-by-breath computed flow-volume loop and thyroarytenoid muscle expiratory EMG as evidence of active expiratory glottic adduction. We found that hypoxia induced a biphasic ventilatory response, with an early peak and a subsequent decrease, and that active expiratory glottic adduction was absent during baseline room-air breathing and hypoxia. We also found that the glottic

abductor phasic inspiratory and tonic expiratory EMG as well as the abdominal muscle phasic expiratory EMG, all of which were present during baseline recording, increased during hypoxia. We conclude that hypoxia does not induce expiratory glottic closure in the very first days of life in awake lambs. Apparently, the ventilatory response to hypoxia in this period already involves an increase in the inspiratory and expiratory glottic aperture, thereby facilitating the high levels of airflow created by the contracting thoracic pump muscles. (*Pediatr Res* 37: 482–488, 1995)

Abbreviations

CT, cricothyroid muscle
EMG, electromyographic activity
 F_{iO_2} , fraction of inspired O_2
 P_{aCO_2} , arterial blood CO_2 tension
PCA, posterior cricoarytenoid muscle
TA, thyroarytenoid muscle
 T_{TA} , time period of enhanced TA expiratory EMG
 $\dot{V}_E$, minute ventilation
 V_T , tidal volume

It has generally been accepted that active expiratory glottic adduction is an essential component of the neonatal response to hypoxia. This expiratory flow-braking mechanism supposedly increases the end expiratory lung volume, thus optimizing the alveolar blood gas exchange. This concept was largely derived from the clinical observation of expiratory grunting in hypoxic neonates with respiratory distress syndrome (1). However, studies of the laryngeal response to hypoxia in early life have yielded conflicting results. Although previous researchers have found an active expiratory glottic adduction in response to hypoxia in neonatal lambs (2, 3), we recently showed that hypoxia ($F_{iO_2} = 0.08$ during 15 min) did not enhance the expiratory EMG of the TA—a glottic adductor muscle—in 11-

to 22-d-old awake lambs (4). Although our results are in agreement with data obtained in adult life (5–7), they were obtained in 11- to 22-d-old lambs with mature peripheral chemoreceptors. We therefore hypothesized that the active expiratory glottic adduction in response to hypoxia might be a unique feature of the very early postnatal period. This hypothesis was in keeping with our demonstration that peripheral chemoreceptor activity, which is low at birth, appears to inhibit TA activity in 11- to 22-d-old lambs (4). Moreover, our hypothesis would reconcile the apparent discrepancy between our results (4) and those obtained by Coté *et al.* (3) in lambs younger than 3 d.

The present study was thus conducted to test the hypothesis that hypoxic lambs in the early postnatal period react to hypoxia by actively closing the glottis during expiration. We also studied the response of glottic abductor and abdominal muscles to hypoxia so as to obtain further insights into the response to hypoxia during early life.

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METHODS

Animals

Twenty-two lambs were enrolled in the study. Because of tachypnea (more than 100 breaths/min) during baseline room-air breathing in seven, we report the results in only 15 lambs. It should be noted, however, that the laryngeal response to hypoxia was qualitatively similar in the 22 lambs studied.

The lambs that underwent surgical preparation (see below) were born in our animal quarters so that surgery could be performed in the very first hours after birth. All lambs were boarded with their mothers in our animal quarters before the experiment. On the day of the experiment, two lambs were in their first 24 h of postnatal life, 10 were between 24 and 48 h old, and three were in their third day of life. Their mean ($\pm$ SD) weight was 4.25 ± 2.28 kg (range 2.4–7.9 kg). The local ethics committee for animal research at our institution approved the protocol of the study.

Surgical Preparation

The day before the experiment, 10 of the 15 lambs underwent a surgical procedure to place intramuscular electrodes. The details of the procedure have been described elsewhere (4, 8). Briefly, under direct vision, we inserted an intramuscular bipolar electrode (enameled chrome wire, 0.7-mm diameter, Chromel, GTSM, Castelnau-d'Audoubert, France) into the TA of the 10 lambs via a window cut in the thyroid cartilage. Electrodes were also inserted in other intrinsic laryngeal muscles: in the PCA (four lambs) after rotation of the larynx, through an incision made in the inferior pharyngeal constrictor; and in the CT (five lambs) (8). Another electrode was placed in the superficial oblique external abdominal muscle of four lambs (9). The leads were subcutaneously tunneled to exit on the back of the animals. The animals received one dose of antibiotics (penicillin and gentamicin) after surgery. The placement of the electrodes was confirmed by a systematic autopsy after completion of the experiment.

In 10 lambs, we also inserted a catheter into the brachial artery for arterial blood gas sampling. Blood gas values were corrected for the rectal temperature of the lamb (Mon-a-Therm 6500, St. Louis, MO) (10).

Measurement Apparatus

The measurement apparatus used has been described in our previous studies (4). Briefly, we attached a face mask, specifically designed for each lamb, to a size 0 pneumotachograph (Hewlett-Packard 21070B, plus Hewlett-Packard 8815A respiratory integrator, Hewlett-Packard, Palo Alto, CA). The Fio_2 , delivered through a T piece at a constant gas flow, can be switched between 0.08, 0.21, and 1.00 in less than 1 s (21049 and P314 Collins valves). We used a mass spectrometer (Perkin-Elmer MGA 1100) to continuously measure the Fio_2 delivered to the lamb and to monitor end-tidal CO_2 at the mask. The laryngeal and abdominal muscle EMG signals were amplified and 30- to 1000-Hz band-pass filtered (Grass P511 AC preamplifier, 7DA DC driver amplifier, Grass Instrument Co., Quincy, MA) before undergoing a 100-ms moving time aver-

aging (Department of Electronics, Faculty of Medicine, University of Sherbrooke, Quebec, Canada). Our integrator has parallel outputs for a chart recorder and a computer. An eight-channel polygraph (Grass 7D, Grass Instrument Co.) recorded the instantaneous airflow, the $\dot{V}_T$, the Fio_2 , and the raw and integrated EMG signals. An IBM-compatible microcomputer (Televideo TeleCAT-286) analyzed the instantaneous airflow, the integrated EMG signals, and the Fio_2 at a 40-Hz sampling rate. The collected data were stored on disk for further analysis.

Design of the Study

The design of the study protocol allowed us to infer the role of hypoxia on TA EMG activity in awake lambs in the very first postnatal days. We could also study the coordination between the TA muscle, glottic abductor muscles, and abdominal muscles during hypoxia at this early age. Also, we could evaluate the differential role of central and peripheral chemoreceptors during hypoxia. This last evaluation was accomplished 1) by having each lamb inhale pure O_2 during five inspirations (Dejours' test), thereby transiently withdrawing the peripheral chemoreceptor function; and 2) by comparing in the same lamb ($n = 4$) the responses to hypocapnic and isocapnic hypoxia.

Our study was done with each lamb positioned in a sling during quiet wakefulness. After applying the face mask and carefully positioning the head, we gave each lamb at least 10 min to adjust to the mask. Between the two hypoxic runs, we allowed the lambs sufficient time to regain baseline prehypoxic ventilation and arterial blood gas values.

Hypocapnic hypoxia test. The hypocapnic hypoxia test has been described elsewhere (4). Briefly, we recorded baseline room-air ventilation for 3 min, before abruptly switching the animal to 0.08 Fio_2 for a hypoxic period of 15 min. During that 15-min hypoxic period, we performed a Dejours' test at the 6- and 12-min marks. We then abruptly switched the animal from 0.08 Fio_2 back to room air for 3 min of recording. The entire test was completed in 21 min.

Isocapnic hypoxia test. The design of this second test was identical to that just described, except that we carefully maintained the isocapnia by continually adding CO_2 to the inspiratory gas mixture. We adjusted the amounts of added CO_2 in light of the continual monitoring of end-tidal CO_2 and the measuring of Paco_2 at 3-min intervals.

Data Analysis

Response to hypoxia. We computed $\dot{V}_E$, $\dot{V}_T$, and breathing frequency for each breath. Averages were calculated over 15 s during the baseline recording; during hypoxia at the moment of the peak ventilatory response; at the 6-, 9-, 12-, and 15-min marks of hypoxia; and finally, 2 min after the return to room-air breathing. We carefully observed the TA EMG, together with the EMG of the other studied muscles, throughout each experimental procedure. We looked for simultaneous expiratory airflow braking in the shape of the flow-volume curves computed breath by breath during the above-defined 15-s epochs in each lamb.

Figure 1. Breath-by-breath computed flow-volume curve obtained in a lamb during baseline room-air breathing (A) and at the 6 min- (B) and 12 min- (C) marks of hypoxia. Note the absence of an abrupt decrease in the expiratory flow that could have suggested airflow braking by glottic closure.

Response of TA and other respiratory muscles to Dejours' test. For each Dejours' test conducted during hypoxia, we calculated the T_{TA} (s) after O_2 inhalation. We also observed the response to O_2 inhalation of the other muscles under study. In addition, we examined the influence of $Paco_2$ by comparing the T_{TA} obtained during the hypocapnic and isocapnic hypoxia tests in the four lambs studied in both conditions.

Statistical Analysis

The ventilatory parameters obtained during the hypocapnic hypoxia tests were compared via an analysis of variance for repeated measures, completed by contrast comparison of the means (Superanova, Abacus Concepts, Berkeley, CA).

$p < 0.05$ was considered significant.

RESULTS

Baseline Room-Air Breathing

Ventilation. During baseline room-air breathing for the 15 lambs, mean $\dot{V}_E$ was $724 \pm 168 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (mean $\pm$ SD), mean V_T was $12.9 \pm 3.1 \text{ mL} \cdot \text{kg}^{-1}$, and mean breathing frequency was $59 \pm 17 \text{ min}^{-1}$. Arterial blood gas values in the 10 lambs with an arterial line were: arterial blood O_2 tension = $10.1 \pm 1.6 \text{ kPa}$; $Paco_2 = 5.7 \pm 0.6 \text{ kPa}$; and $pH = 7.37 \pm 0.06$. None of the 15 lambs showed any expiratory airflow braking on the airflow traces or the breath-by-breath computed flow-volume curves (Fig. 1A).

TA muscle activity. The TA EMG was continuously recorded in 10 lambs. During baseline room-air breathing, the TA was largely inactive in eight lambs, apart from the swallowing movements (Figs. 2A and 3A). In the other two lambs, a small-amplitude phasic inspiratory EMG was consistently recorded from the TA electrode. No TA phasic expiratory EMG was observed in any of the 10 lambs.

Glottic abductor muscle and abdominal muscle activity. In the four lambs whose PCA (glottic abductor muscle) was studied and in the five lambs whose CT (synergistic to the PCA for the inspiratory glottic abduction) was studied, we observed consistent phasic inspiratory and tonic expiratory EMG in both glottic muscles (Figs. 2A and 3A). In the four lambs whose external oblique abdominal muscle was studied, a phasic expiratory abdominal muscle EMG was consistently observed, the amplitude varying with the body movements (Fig. 3A).

Figure 2. TA and CT EMG activities during baseline room-air breathing (A) and hypoxia (B). TA, raw TA EMG; fTA, moving time averaged TA; $\dot{V}$, instantaneous airflow, inspiration upwards; CT, raw CT EMG; fCT, moving time-averaged CT. Note the absence of expiratory TA contraction during normoxic breathing and 0.08 F_{iO_2} breathing, and the increase in baseline phasic inspiratory and tonic expiratory CT EMG with 0.08 F_{iO_2} breathing. Switching off the peripheral chemoreceptor activity with five breaths of pure O_2 ($F_{iO_2} = 1$, Dejours' test) during hypoxia triggers a decrease in ventilation with decreased CT EMG; simultaneously, an expiratory airflow braking related to active glottic adduction (see TA traces) is observed.

Figure 3. TA, PCA, and abdominal muscle EMG activities during baseline room-air breathing (A) and hypoxia (B). See Figure 2 for definition of abbreviations. PCA, raw PCA EMG; $\int \text{PCA}$, moving time-averaged PCA; ABD, raw abdominal muscle EMG; $\int \text{ABD}$, moving time-averaged ABD. During baseline room-air breathing, while TA contraction is absent, PCA phasic inspiratory and tonic expiratory EMG activities are present and ABD phasic expiratory EMG is recorded. Hypoxia ($\text{FiO}_2 = 0.08$) enhances PCA and ABD EMG activities, but no active expiratory glottic adduction is observed. On the contrary, switching off the peripheral chemoreceptor activity with five breaths of pure O_2 ($\text{FiO}_2 = 1$, Dejours' test) triggers a decrease in ventilation with decreased PCA and ABD EMG, and TA expiratory contraction with expiratory airflow braking for several respiratory cycles.

Hypoxic Breathing

Ventilation. Results of the hypocapnic hypoxic test, completed in all the lambs, showed a diphasic $\dot{V}_E$ response to hypocapnic hypoxia, in the 15 awake, 1- to 3-d-old lambs; that is, an early maximum in the first 3 min of hypoxia followed by a decrease to a plateau. During the entire hypoxic period, however, $\dot{V}_E$ was significantly higher than the prehypoxic value (Fig. 4). Both the $\dot{V}_T$ and breathing frequency during the hypoxic period had a time course similar to that of hypocapnic hypoxia—an early maximum and a subsequent decrease—although the breathing frequency tended to be more sustained than $\dot{V}_T$ (Fig. 4). Blood gas measurements at the 6-min mark of hypoxia in all 10 lambs with an arterial line yielded the following mean values: arterial blood O_2 tension = 2.7 ± 0.5 kPa; Paco_2 = 4.6 ± 0.5 kPa; and pH = 7.47 ± 0.06 .

The response of the four lambs studied during isocapnic hypoxia appeared to be somewhat higher and more sustained than that occurring during hypocapnic hypoxia. The $\dot{V}_E$ response to an FiO_2 of 0.08 for 15 min during both hypocapnia and isocapnia is illustrated in Figure 5.

TA muscle activity and flow-volume curves. Our systematic and careful examination of the EMG signals throughout the hypocapnic hypoxic test consistently showed no expiratory recruitment of the TA in any of the 10 lambs (Figs. 2B and 3B). Moreover, close observation of the flow traces and computed

flow-volume loops of the 15 lambs showed that expiratory flow braking was absent throughout the 15-min hypoxic test in all 15 lambs (Fig. 1B and C). As for the TA inspiratory phasic EMG, if it was present during baseline room-air breathing (two lambs), it was enhanced during hypoxia.

The results were qualitatively similar during isocapnic hypoxia, for both the TA in the three lambs and the flow-volume loop in the four lambs studied in both hypo- and isocapnic hypoxic conditions.

Glottic abductor and abdominal muscles. During hypoxia, consistent enhancement of PCA (four lambs) and CT (five lambs) EMG was observed for both the inspiratory phasic and tonic expiratory EMG (Figs. 2B and 3B). Also, in the four lambs whose abdominal muscle EMG were studied, we observed a consistent increase in abdominal muscle expiratory phasic EMG (Fig. 3B).

Response to Dejours' test during hypoxia. In the 15 lambs during hypocapnic hypoxia, the ventilation decreased within 3 to 4 s after the inhalation of pure O_2 . The decrease in ventilation varied, however, from one lamb to another: whereas in 12 lambs the Dejours' test induced a mild decrease in $\dot{V}_T$ as well as in breathing frequency, in three lambs we observed a central apnea (duration of 3 to 10 s). Concurrent with the decrease in ventilation, TA expiratory EMG appeared in five of the seven lambs; it then progressively faded when the ventilation re-

Figure 4. Ventilatory response to 15 min hypocapnic hypoxic breathing ($FiO_2 = 0.08$) in 15 awake lambs during the first 3 postnatal days. Bars = SD. * $p < 0.05$ vs baseline; † $p < 0.05$ vs peak.

gained the pre-Dejours' test level (Figs. 2B, 3B, and 6A). Also, tonic TA EMG was observed throughout the central apnea in two of the three lambs, changing to expiratory EMG for the first few breaths after resumption of breathing. The time period T_{TA} of enhanced TA expiratory (and continuous, when present) EMG for the 10 lambs was 12.9 ± 10 s (range 0 to 33 s). Close observation of the airflow trace and the breath-by-breath computed flow-volume loop showed that an expiratory flow braking paralleled the presence of TA expiratory EMG (Figs. 2B, 3B, and 6A).

During isocapnic hypoxia, the decrease in ventilation in response to the Dejours' test was consistently less marked than that which occurred during hypocapnic hypoxia in the four lambs studied in both conditions. Similarly, the TA response was absent or markedly reduced during isocapnic hypoxia

Figure 5. Ventilatory response to 15 min of hypoxic breathing ($FiO_2 = 0.08$) in four awake lambs in hypocapnic and isocapnic conditions. Bars = SD.

($T_{TA} = 6.3 \pm 3$ s) compared with the response of the same lambs during hypocapnic hypoxia ($T_{TA} = 24.3 \pm 8$ s) (Fig. 6).

The decreased ventilation in response to the Dejours' test during hypoxia was accompanied by a parallel decrease in PCA and CT EMG for both the inspiratory and expiratory components (Fig. 2B and 3B). When central apnea and continuous TA EMG were present, both PCA and CT EMG were absent throughout central apnea. Although the inspiratory activity of both muscles progressively increased with resumption of breathing, the disappearance of TA expiratory EMG led to a resumption of tonic expiratory EMG of both the PCA and CT (Figs. 2B and 3B).

A decrease in the abdominal muscle EMG was also observed in response to the Dejours' test in the four lambs undergoing this testing. This decrease paralleled the ventilatory response to Dejours' test (Fig. 3B). During central apnea, no abdominal muscle EMG was recorded in any of the four lambs.

DISCUSSION

The striking finding of this study is that, contrary to current thinking, hypoxia does not lead to active expiratory airflow braking in awake, nonsedated lambs during the first 3 postnatal days.

It has been commonly stated that the fight against hypoxia during the first days of life relies primarily on active expiratory airflow braking. This hypothesis first originated with the audible expiratory grunting heard in hypoxic preterm newborns during the respiratory distress syndrome (1); it was later supported by results from studies of the early postnatal period in mammals, during both normoxic and hypoxic breathing. First, an active expiratory airflow laryngeal braking was recorded during room-air breathing in premature (11) and term (12–14) humans, and more recently in premature lambs delivered by caesarean section (15). In these studies, however, the active expiratory airflow laryngeal braking was clearly observed only during the first minutes after birth; it disappeared thereafter. Second, hypoxia was reported to enhance TA expiratory EMG in tracheostomized lambs during quiet sleep (2) or to trigger an expiratory airflow braking in lambs during their first 3 d of life (3). At this point, the common understanding of the response to

Figure 6. Ventilatory and TA response after pure O_2 inhalation during hypocapnic hypoxia (A) and isocapnic hypoxia (B). Abrupt fall in ventilation with marked enhancement of TA EMG is only observed in hypocapnic hypoxia.

hypoxia during the early postnatal period was that, by actively closing the glottis, the newborn mammal induced an expiratory airflow braking that eventually served both to increase the end-expiratory lung volume and to enhance the oxygen extraction by the pulmonary blood (3, 16). With its involvement of the small intrinsic laryngeal muscles and its low cost in terms of energy requirements, this mechanism—the so-called intrinsic positive end expiratory pressure—appeared particularly suited to the hypoxic newborn mammal in the first hours of life (3, 16).

Recent data from our laboratory, however, challenge this concept. Indeed, we have shown that hypoxia in awake, non-sedated lambs more than 10 d old does not lead to active expiratory glottic adduction (4). In the same study, by partitioning the effects of the various controllers of the TA activity during hypoxia, we were able to show that the stimulation of the peripheral chemoreceptors in lambs more than 10 d old has an inhibitory influence on expiratory TA EMG, as reported in adult mammals as well (7). To reconcile our results in awake lambs more than 10 d old (4) with the results obtained in awake lambs less than 72 h old (3), we hypothesized that the postnatal maturation of the peripheral chemoreceptor function might explain both the more sustained ventilatory response to hypoxia and the disappearance of the active glottic adduction enhancement by hypoxia (4).

On the contrary, the present data drawn from a direct recording of the TA—a representative glottic adductor mus-

cle—show that hypoxia does not lead to active expiratory glottic adduction in awake, non-sedated, very young lambs. Our data for lambs at different postnatal ages (present study and 4) and other investigators' data for adult mammals (5, 6) suggest that from the beginning of postnatal life and into adult life mammals do not use active expiratory glottic adduction to fight against hypoxia. However, because TA expiratory activity has been shown to be invariably present in non-sedated puppies during room-air breathing (17), the absence of TA activity enhancement by hypoxia needs to be confirmed in newborn mammals that are less mature than the lamb at birth.

It has been previously reported that the laryngeal response in hypoxia involves an inspiratory and expiratory glottic abduction that facilitates high levels of airflow in both respiratory phases. Indeed, an increased active inspiratory glottic abduction has been observed during hypoxia in awake and sleeping dogs (5), adult decerebrate cats (18), and awake humans (19–21). In the present study, we observed that hypoxia increases inspiratory phasic EMG in both the PCA (the glottic abductor) and CT [synergistic to the PCA for the inspiratory glottic abduction (22)], in agreement with those previous results. Moreover, our observation that in hypoxia, when TA EMG is absent, the expiratory tonic EMG activity of both PCA and CT is enhanced suggests that the laryngeal aperture is increased during expiration with hypoxia compared with normoxic breathing. Previous findings by other investigators showed that hypoxia does induce a glottic widening, not only in inspiration, but also in expiration (5, 6, 18–20). Apparently, expiratory widening of the glottis, together with the increase in the expiratory phasic EMG of the abdominal muscles, constitutes a well-coordinated response to hypoxia that is already functional at birth in lambs and is qualitatively identical to the response previously reported by us in lambs more than 10 d old (9).

Finally, our observations shed some light on the role of the various controllers of the laryngeal muscles during the first days of life. The unmasking of TA expiratory EMG—or even the continuous EMG when apnea was observed—by transient inhalation of pure O_2 (Dejours' test) during hypocapnic hypoxia suggests that the stimulation of the central inspiratory drive by the peripheral chemoreceptors themselves in newborn lambs inhibits the glottic adductor muscles. Similarly, the decrease—and even the disappearance when apnea was present—of both the PCA and CT activity after the Dejours' test in hypoxia suggests that the stimulation of the peripheral chemoreceptors is responsible for an increased phasic and tonic EMG of glottic abductor muscles. Moreover, the differences in the results obtained in hypocapnic hypoxia and isocapnic hypoxia suggest that the decreased afferents from the central chemoreceptors in the hypocapnic run stimulate the expiratory glottic adduction but inhibit the contraction of the glottic abductors. The above results are qualitatively similar to the results we obtained in awake, non-sedated lambs more than 10 d old, although the effect of the peripheral chemoreceptors during hypoxia is obviously much less during the first postnatal days (23). Our results do not permit us to discuss the potential participation of the potent vagal influences (24) in the inhibi-

tion of the active expiratory glottic adduction during hypocapnic hypoxia.

The reasons for the discrepancies between the present data and those obtained in two previous studies in lambs (2, 3) are not clear. The presence of a fenestrated tracheostomy tube and/or the different sleep state (quiet sleep *versus* wakefulness) could account for the enhanced TA activity during expiration in the study by Johnson and Fewell (2). On the other hand, the expiratory airflow braking observed in some lambs during hypoxia by Coté *et al.* (3) might well be due to the postinspiratory activity of the diaphragm. Although our study was not designed to answer this question, recent data obtained in kittens render such explanation possible (25).

In conclusion, our results show that hypoxia, with either hypocapnia or isocapnia, is not responsible for an active expiratory glottic closure in lambs during the very first days of life. Conversely, the response to hypoxia during this early period in lambs involves active glottic abduction during both inspiration and expiration. As for the expiratory grunting manifested by the preterm neonate during the respiratory distress syndrome, preliminary results from our laboratory indicate that it could be related to the excess of pulmonary fluid known to be present in this situation (26).

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