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Mechanisms of active laryngeal closure during noninvasive intermittent positive pressure ventilation in nonsedated lambs

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R E S U L T S

Mechanisms of active laryngeal closure during noninvasive intermittent positive pressure ventilation in nonsedated lambs. J Appl Physiol 105: 1406–1412, 2008. First published August 14, 2008; doi:10.1152/japplphysiol.90727.2008.—The present study stems from our recent demonstration (Moreau-Bussière F, Samson N, St-Hilaire M, Reix P, Lafond JR, Nsgebe E, Praud JP. J Appl Physiol 102: 2149–2157, 2007) that a progressive increase in nasal intermittent positive pressure ventilation (nIPPV) leads to active glottal closure in nonsedated, newborn lambs. The aim of the study was to determine whether the mechanisms involved in this glottal narrowing during nIPPV originate from upper airway receptors and/or from bronchopulmonary receptors. Two groups of newborn lambs were chronically instrumented for polysomnographic recording: the first group of five lambs underwent a two-step bilateral thoracic vagotomy using video-assisted thoracoscopic surgery (bilateral vagotomy group), while the second group, composed of six lambs, underwent chronic laryngotracheal separation (isolated upper airway group). A few days later, polysomnographic recordings were performed to assess glottal muscle electromyography during step increases in nIPPV (volume control mode). Results show that active glottal narrowing does not develop when nIPPV is applied on the upper airways only, and that this narrowing is prevented by bilateral vagotomy when nIPPV is applied on intact airways. In conclusion, active glottal narrowing in response to increasing nIPPV originates from bronchopulmonary receptors.

MATERIALS AND METHODS

Experiments were conducted in 14 mixed-bred lambs aged from 2 to 6 days and weighing 4.1 kg (SD 0.8; range 2.9–5.4) on the experimental day. All lambs were born at term by spontaneous vaginal delivery. The study was approved by the ethics committee for animal care and experimentation of the Université de Sherbrooke.

Surgical Preparation

Common instrumentation. Aseptic surgery was performed in all lambs at 1–2 days of life under general anesthesia (2% isoflurane + 30% N2O + 68% O2), after an intramuscular injection of atropine sulfate (0.1 mg/kg), ketamine (10 mg/kg), and antibiotics (5 mg/kg gentamicin and 7,500 IU/kg Duplocillin). One dose of ketoprofen (3 mg/kg im) was given immediately before surgery for analgesia and repeated if needed on the next day. Chronic instrumentation was performed as previously described (11, 21). Briefly, bipolar electrodes were inserted into the TA muscles (a glottal constrictor) and CT muscles (a glottal dilator) for recording EMG activity. Two needle electrodes were inserted into the parietal cortex through the skull, for electroencephalogram (EEG) recording. One scalp electrode served as a ground. Finally, a catheter was placed into the brachial artery for measuring pH and blood gases. Heart rate, rectal temperature, pulse oximetry, end-tidal CO2, and blood pH were continuously monitored throughout surgery. Postoperative care included daily intramuscular injection of 5 mg/kg gentamicin and 0.05 ml/kg duplocilline until the end of the experimentation.

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Surgical instrumentation for bilateral vagotomy. Eight of the 14 lambs underwent a two-step, intrathoracic bilateral vagotomy, which first involved video-assisted thorascopic surgery (Karl Storz, Tuttingen, Germany). After generating a right pneumothorax by CO₂ insufflation, the endoscope and surgical instruments were introduced into the pleural space through two small (5–10 mm) parietal incisions. The bare portion of an enameled chrome wire (0.12-mm diameter, Leico Industries, New York, NY) was positioned around the vagus nerve, just caudally to the origin of the recurrent laryngeal nerve. The remaining enameled wire was glued in polyethylene tubing, with the two ends exiting through the skin. Once completed on the right side, the same procedure was repeated on the left. Finally, 2–5 days after surgery, a bilateral vagotomy was performed, using a procedure previously described for the superior laryngeal nerve (3). The two bare ends of chrome wire protruding from the right thorax were attached to an electrocauter (model 770, Electrosectilis, Brichter, CA). Traction was then applied to the wire during electrocauterity, thus sectioning the vagus nerve. The procedure was completed in <5 s and resulted in minimal discomfort for the lamb (startle at most). The procedure was then repeated on the left side. Bilateral vagotomy was confirmed by pulling off the unbroken wires from the thorax just after electrocautery, 2) by immediately observing a decrease in respiratory rate (RR), and 3) by systematic verification at necropsy. This unique model allowed studying the same lambs before and after bilateral vagotomy, with each lamb acting as its own control.

Surgery for the isolated upper airway group. The remaining six lambs underwent chronic separation of their upper airways from lower airways. The separation was performed directly under the larynx, just above the first tracheal ring. The caudal end of the larynx was attached to a 2-cm-long Dacron aortic prosthesis, whose caudal end was attached to a neck stoma. In addition, a tracheostomy was performed between the fifth and sixth rings of the trachea. A 2-cm-long endotracheal tube was sutured and glued externally around the tracheostomy, in such a way that there was no permanent endotracheal tube. Finally, the rostral end of the trachea was sutured. Using this chronic, nonsedated animal model with isolated upper airways is unique.

Experimental Equipment

Ventilatory equipment. Intermittent positive pressure ventilation was performed using a Siemens Servo 300 ventilator and Servo Screen (Siemens, New York, NY) with heated (32°C) and humidified air. Nasal ventilation was performed through a custom-designed nasal mask, as previously described (11). Briefly, the mask was built from dental paste to best fit the muzzle of each lamb. A small, nondiffusing gas bag (200 ml) was attached to the external end of the Dacron tube, as a surrogate for the lamb’s lungs.

Recording equipment. Just before polysomnographic recordings, two needle electrodes were inserted subcutaneously for electrooculogram (EOG) recording. A pulse oximeter (O₂ saturation from pulse oximetry) probe was also attached at the base of the tail. In addition, elastic bands for respiratory inductance plethysmography (Respiritace, NIMS, Miami Beach, FL) were installed on the thorax and the abdomen to monitor respiratory movements and assess lung volume variations qualitatively. Mask pressure was monitored by using calibrated pressure transducers (MP 45-30-871, Validyne, Northridge, CA). All recordings were carried out in nonsedated lambs, using our custom-designed radiotelemetry system. The transmitter used for this study was composed of differential channels (EEG, EOG, ECG, and 4 EMGs) (8, 9). The raw EMG signals were sampled at 500 Hz, rectified, integrated, and moving time averaged (100 ms). Polysomnographic signals were recorded on a PC using Acknowledge software (version 3.7.3, BioPac Systems, Santa Barbara, CA).

Design of the Study

On arrival in our in-house animal quarters, only lambs of the bilateral vagotomy group were housed with their mother. Lambs from the isolated upper airway group were housed in a Plexiglas chamber (1.2 m³, as recommended by the Canadian Council for Animal Care for sheep housing). Water-saturated air was continuously flowed (10 l/min) through the chamber using an Allegiance Airlife Nebulizer (no. 5207) and a home humidifier. Tracheal secretions were systematically suctioned at least three times a day (20). Lambs from this group were fed ad libitum three times a day with ewe’s milk. The study was performed without sedation at least 48 h after surgery. The study was designed to allow simultaneous recording of EEG, EOG, and EMG activity, mask pressure, respiratory movements, and O₂ saturation from pulse oximetry while using incremental levels of ventilation during wakefulness (W) and quiet sleep (QS). The lambs were comfortably positioned in a sling with loose restraints. Two experimenters were present throughout the recordings to note lamb behavior.

Bilateral vagotomy group. A first polysomnographic recording was performed during nasal ventilation with the vagi intact (= instrumented but not cut). On the following day, the recording was repeated after bilateral vagotomy. The protocol design for nasal ventilation has been previously described (11). An initial recording was performed with the nasal mask on but with no CPAP (continuous positive airway pressure). Thereafter, “baseline” tidal volume (VT) and RR were obtained with a CPAP of 4 cmH₂O (CPAP 4) applied via the nasal mask. Three levels of ventilation were tested in the VC mode, while maintaining a positive end-expiratory pressure at 4 cmH₂O. For the first level of VC ventilation (VC 1), VT and RR were set at the values recorded when the lamb was breathing spontaneously with CPAP 4. Thereafter, VT was increased in a stepwise manner to 10 ml/kg (VC 2) and 15 ml/kg (VC 3). Approximately 100 respiratory cycles were recorded at each level of ventilation during both W and QS. Mechanical ventilation was halted if the lamb displayed discomfort or agitation and/or there was an abdominal distension or presence of liquid reflux via the nasogastric tube. While both the VC mode and pressure support IPPV were tested in our laboratory’s previous study (11), only the VC mode was tested in the present study. Indeed, pressure support was not feasible on isolated upper airways (no inspiratory trigger from the lamb to the ventilator).

Isolated upper airway group. Two polysomnographic recordings were performed on the same day in random order, during nasal mask and tracheostomy ventilation. Each IPPV level was tested as described for the bifagotomy group. After completion of the first round of ventilation via the nasal or tracheostomy route, the lambs rested for 30 min before the protocol was repeated on the other portion of the airways.

Data Analysis

States of alertness. Standard electrophysiological and behavioral criteria were used to define W, QS, and active sleep from EEG, EOG, and continuous observation (16).

Respiratory parameters. Twenty consecutive breaths, which had to be preceded and followed by 20 s of stable respiratory pattern, were selected for analysis at every ventilatory level in W and QS. Inspiratory duration was defined as the insufflation time by the mechanical ventilator on the mask pressure trace, except when IPPV was applied on the isolated upper airways (see below). Amplitude of the inspiratory TA and CT EMGs was analyzed and averaged, using Acknowledge software. The maximal amplitude of the phasic inspiratory CT EMG measured in W and in the no-CPAP condition was averaged and used as a reference value (100%) for all subsequent measurements of CT EMG in each lamb. As, typically, no phasic TA EMG was recorded during inspiration, the maximal amplitude of the phasic TA
EMG was averaged from four swallowing activities and used as the reference value (100%) for subsequent measurements of TA EMG. Of note, when IPPV was applied on the isolated upper airways, phasic inspiratory CT EMG and expiratory TA EMG were still present with spontaneous breathing via the open tracheostomy, irrespective of the timing of mechanical insufflations. Hence, a different analysis was necessary for the 20 breaths selected as above during stable respiration via the tracheostomy. First, the number of mechanical insufflations with inspiratory CT or TA EMG was counted. Thereafter, the cycles with phasic CT or TA EMG obviously occurring with spontaneous inspiration or expiration, respectively, were then discarded. When in doubt, the cycles were not discarded. Finally, the number of mechanical insufflations with phasic inspiratory CT or TA EMG was expressed as a percentage of the total number of mechanical insufflations.

**Statistical analysis.** Amplitude of TA and CT EMG was first averaged in each lamb for each ventilation step, each experimental condition and W or QS, and then in all lambs as a whole. Results were finally expressed as a mean with SD. Statistical analyses were conducted using generalized estimating equations (GENMOD procedure of SAS software, version 8) for repeated measures and Poisson distribution. The working correlation matrix was of the exchangeable type. A difference was deemed statistically significant, if \( P \) value was \(<0.05\).

**RESULTS**

Since results for inspiratory TA and CT EMGs were not significantly different between W and QS in both the current study (W vs. QS: inspiratory TA EMG, \( P = 0.83 \); inspiratory CT EMG, \( P = 0.51 \)) and our laboratory’s previous study (11), results obtained in both states of alertness are reported together.

### Lambs with Bilateral Vagotomy

From a total of eight lambs, which initially underwent surgery, the study was completed in five lambs, due to technical problems with chronic electrodes or the vagotomy, which was not complete on one side. Total duration of polysomnographic recordings was 392 min.

With intact vagi, and while breathing with the nasal mask on but without CPAP, regular phasic inspiratory CT EMG was consistently observed in all five lambs. By contrast, phasic TA EMG was observed during expiration only for most respirations in two lambs, but more irregularly in the remaining three lambs. Moreover, no phasic inspiratory TA EMG was observed in any of the lambs (Fig. 1). Overall, CT and TA EMG were not modified after bilateral vagotomy, while on no CPAP (Table 1). While inspiratory TA EMG was still absent when changing from no CPAP to CPAP 4 breathing before bilateral vagotomy, a significant decrease in inspiratory CT EMG followed the application of nasal CPAP 4 (\( P = 0.003 \)). However, inspiratory CT EMG was still consistently present with CPAP 4. Moreover, expiratory TA EMG was only present in one lamb. Similar changes were observed when switching from nasal no CPAP to CPAP 4 after bilateral vagotomy, i.e., no inspiratory TA EMG, and a significant decrease in inspiratory CT EMG (\( P = 0.009 \)) (Table 1).

The progressive increase in nasal ventilation before bilateral vagotomy was paralleled by an increase in inspiratory TA EMG, in phase with mechanical insufflations (\( P = 0.05 \), VC 2 vs. CPAP 4) (Fig. 2). Conversely, inspiratory CT EMG de-

![Fig. 1. Electrical activity (electromyogram (EMG)) of thyroarytenoid (TA; a laryngeal constrictor) and cricothyroid (CT; a laryngeal dilator) muscles in one lamb during baseline breathing (no continuous positive airway pressure (CPAP); left) and nasal intermittent positive pressure ventilation (nIPPV) before (middle) and after (right) bilateral vagotomy. Recordings were obtained during quiet sleep. Note: 1) the increase in TA EMG during inspiration (I) from no CPAP to nIPPV before bilateral vagotomy; 2) the absence of an increase in TA EMG after bilateral vagotomy; 3) the decrease in respiratory rate after bilateral vagotomy on the sum signal. TA, TA muscle EMG; CT, CT muscle EMG; \( \overline{fCT} \), moving time-averaged CT; SUM, sum signal of the respiratory inductance plethysmograph, illustrating the variations of lung volumes with respiration (inspiration upward); EEG, electroencephalogram; EOG, electrooculogram.](http://Jap Physiology.org) at Unr De Sherbrooke on August 28, 2012
Mechanisms of Glottal Closure During Nasal Ventilation

Table 1. Mean values of TA (laryngeal constrictor) and CT (laryngeal dilator) EMG activity and respiratory parameters during no CPAP, 4-cmH2O CPAP, and volume-controlled ventilation via the nasal route in the bilateral vagotomy group and via the tracheostomy in the isolated upper airway group

<table>
<thead>
<tr>
<th>Bilateral Vagotomy Group Nasal Ventilation</th>
<th>Isolated Upper Airway Group Tracheostomy Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA, %</td>
<td>CT, %</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>No CPAP</td>
<td>7 (2)⁸</td>
</tr>
<tr>
<td>CPAP 4</td>
<td>6 (1)⁸</td>
</tr>
<tr>
<td>VC 1</td>
<td>8 (4)⁸</td>
</tr>
<tr>
<td>VC 2</td>
<td>13 (12)⁸</td>
</tr>
<tr>
<td>VC 3</td>
<td>16 (13)</td>
</tr>
</tbody>
</table>

Values are means (SD). Thyroarytenoid (TA) and cricothyroid (CT) electromyogram (EMG) are inspiratory electrical activity expressed as a percentage of baseline EMG. Vt, tidal volume; RR, respiratory rate; CPAP, continuous positive airway pressure; CPAP 4, 4-cmH2O CPAP; VC 1, 2, and 3: first, second and third level of VC, respectively.

Increased with increased nasal ventilation (P < 0.0001, VC 2 vs. CPAP 4) (Fig. 2).

Following bilateral vagotomy, the increase in inspiratory TA EMG previously observed with increasing nasal ventilation was inhibited (Fig. 3A). However, the decrease in inspiratory CT EMG was still present (P = 0.003, VC 2 vs. CPAP 4) (Fig. 4A). Figure 1 illustrates the effects of bilateral vagotomy on TA and CT EMG in one lamb.

Lambs with Isolated Upper Airways

Total duration of polysomnographic recordings was 586 min in six lambs. Baseline recording was performed with lambs breathing through their tracheostomy, with a nasal mask in place but no CPAP. As expected, regular phasic inspiratory CT EMG, as well as regular phasic expiratory TA EMG, was observed in five lambs. However, no inspiratory TA EMG or expiratory CT EMG was observed (Fig. 5).

Mechanical ventilation applied on the lower airways (via tracheostomy). While the addition of CPAP 4 via the tracheostomy induced no changes in inspiratory TA (P = 0.96), a statistically significant decrease in inspiratory CT EMG was observed (P = 0.0001). Both the expiratory TA EMG and the inspiratory CT EMG were still present in the same five lambs.

The step increase in IPPV via the tracheostomy induced a significant increase in inspiratory TA EMG (VC 2 vs. CPAP 4, P = 0.002). Simultaneously, inspiratory CT EMG significantly decreased (VC 2 vs. no CPAP, P = 0.005) (Fig. 5).

Mechanical ventilation applied on the isolated upper airways (via the nasal mask). Application of nIPPV on the isolated upper airways did not induce any increase in inspiratory TA EMG activity, compared with no CPAP (1.2 vs. 0.4% of breathing cycles, P = 0.5) (Fig. 3B). In addition, inspiratory TA EMG was significantly lower when IPPV was applied upon the isolated upper airways comparatively to that applied on the lower airways via the tracheostomy (1.2 vs. 15% of breathing cycles, P < 0.0001) (Fig. 3B). In addition, no decrease in inspiratory CT EMG activity was noted when IPPV was applied on the isolated upper airways, compared with no CPAP (100 vs. 91% of breathing cycles, P = 0.3) (Fig. 4B). Finally, the percentage of breathing cycles with inspiratory CT EMG was significantly higher when IPPV was applied onto the isolated upper airways as opposed to application on the lower airways via the tracheostomy (100 vs. 18%, P = 0.01) (Fig. 4B). Figure 5 illustrates the differences in TA and CT EMG in one lamb when IPPV is applied on the lower airways vs. on the upper airways.

DISCUSSION

The present study provides new insight on the mechanisms involved in alternations of glottal muscle activity during noninvasive intermittent positive pressure ventilation. Indeed, the results herein suggest that the increase in glottal constrictor muscle EMG observed when increasing nIPPV originates mainly from bronchopulmonary receptors, with no role for upper airway receptors. In addition, results show that the simultaneous decrease in glottal...
dilator muscle EMG does not originate from upper airway or bronchopulmonary receptors. Such unique results obtained in newly developed ovine models further illustrate the influence of lower airway receptors on upper airway function.

**Increase in TA Muscle Inspiratory EMG Activity**

Several results from the present study show that bronchopulmonary receptors are responsible for the increase in inspiratory TA EMG during nIPPV. First, inspiratory TA EMG increases when IPPV is applied via tracheostomy. Second, the increase in inspiratory TA EMG is prevented by bilateral vagotomy, which cuts most vagal afferent messages from bronchopulmonary origin to the brain stem respiratory centers. Finally, the absence of any increase in inspiratory TA EMG when nIPPV is applied on the isolated upper airways strongly argues against the involvement of any type of upper airway receptor.

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**Fig. 3.** The increase in inspiratory TA muscle EMG observed with IPPV originates from bronchopulmonary receptors and not from the upper airways (UA). A: effects of vagotomy. The significant increase in mean inspiratory TA EMG observed when ventilating intact lambs via a nasal mask (left) (P = 0.0008 vs. baseline breathing) is inhibited by bilateral vagotomy (right) (P = 0.4). Voltage amplitude of inspiratory TA EMG is expressed as a percentage of the mean amplitude observed with swallows during baseline recording. The figure illustrates the VC level (either VC 2 or VC 3), where amplitude of inspiratory TA EMG is the highest. B: lambs with isolated UAs. The significant increase in the number of breathing cycles with inspiratory TA EMG observed from noCPAP condition when IPPV is applied solely on the lower airways (LAs) via a tracheostomy (P < 0.0001) vs. baseline breathing) (middle bar; LA-VC) is absent when ventilating the isolated UAs (right bar; UA-VC) (P = 0.5). *P < 0.05.

**Fig. 4.** Decrease in inspiratory CT EMG from baseline breathing to IPPV. A: the observation that the inhibition of inspiratory CT EMG in IPPV is not prevented by vagotomy suggests that this inhibition does not originate from the bronchopulmonary receptors. The figure illustrates the VC level (either VC 2 or VC 3) where amplitude of inspiratory TA EMG is the highest. B: similarly, the observation that the number of breathing cycles with inspiratory CT EMG is still significantly decreased when IPPV is applied on the isolated UAs only suggests that it does not originate from the UAs. *P < 0.05.
Our study was not aimed, however, at determining which type of bronchopulmonary receptor(s) is involved in the increase in inspiratory TA EMG with nIPPV. Both the slowly and rapidly adapting receptors are stimulated by an increase in VT (18). Stimulation of the rapidly adapting receptors is further suggested by the observation of frequent swallows at the highest volumes (VC 3) tested in the present study (18). Further partitioning the responsibility of slowly vs. rapidly adapting bronchopulmonary receptors may prove to be a difficult task, although attempts could be made with oxygen saturation inhalation (via a tracheostomy) (12), after verification that oxygen saturation is also capable of inhibiting slowly adapting receptors in lambs. Finally, we propose the likely noninvolvement of C-fiber endings, since our laboratory previously showed that stimulation of pulmonary C-fiber endings in lambs rather leads to an increase in expiratory TA EMG (2). This hypothesis could be easily tested using our laboratory’s neonatal ovine model with blocked C fibers (2).

Literature data have established that glottal constrictor muscles (e.g., TA muscles) are normally active during the postinspiratory phase of the breathing cycle. This serves to brake expiratory flow and delay lung emptying, a strategy especially used by the newborn in case of lung disease (14). A few studies, however, have reported that TA muscles can, at times, be active in inspiration. That includes one personal observation of simultaneously enhanced EMG activity of both TA and posterior cricoarytenoid muscle (a glottal dilator muscle) during inspiratory efforts against an external airway occlusion (5). From these data, we proposed that TA muscle inspiratory EMG could be synergistic to the posterior cricoarytenoid to induce further glottal dilation in certain conditions. Other researchers suggested that TA inspiratory EMG can be triggered by the stimulation of laryngeal negative pressure receptors (19). Those previous observations during airway occlusion are quite different from the present results, where the CT muscles [glottal dilator muscle in the lamb (17)] are decreased during mechanical insufflations, whereas TA muscle EMG is increased. Hence, our present results showing the involvement of bronchopulmonary receptors are not contradictory with previous results, implicating upper airway receptors (5, 19), for the conditions are quite different, especially with regards to upper airway intraluminal pressure. Finally, we suggest that our present results showing TA inspiratory EMG with IPPV is likely a defense mechanism, which originates from bronchopulmonary receptors and aims at protecting the lung from overdistension.

### Decrease in CT Muscle Inspiratory EMG Activity

Similarly to TA EMG, no significant variation in inspiratory CT EMG was observed when nIPPV was administered directly on the upper airways. This suggests that the decrease in CT inspiratory EMG observed when increasing nIPPV onto intact airways does not originate from upper airway receptors. Moreover, bilateral vagotomy did not prevent the decrease in inspiratory EMG, suggesting that bronchopulmonary receptors are not involved in the inhibition of CT EMG with nIPPV. In addition, results from our laboratory’s previous study suggest that peripheral and central chemoreceptors are not the major actors responsible for this decrease in inspiratory CT EMG (11). Indeed, overall, mean values of arterial blood gases were not modified during the observed decrease in inspiratory CT EMG with increasing nIPPV. Finally, while receptors of the chest wall, such as the neuromuscular spindles or Golgi tendon...
 Validation of Two New Neonatal Ovine Models

A recent review on bronchopulmonary receptors/reflexes has highlighted the importance of gaining further knowledge on the modifications of upper airway function induced by mechanisms originating from the intrathoracic airways and the lungs (1). This is likely to be especially relevant in the neonatal period, where vagal afferent messages originating from bronchopulmonary receptors seem prominent (7). Two animal models were specifically developed for tackling these issues and validated in the present study. In the first model, a two-step bilateral vagotomy enabled us to use each lamb as its own control. Compared with previous bivagotomized lamb models (13, 23), the use of video-assisted surgery is especially attractive, for it is far less invasive and painful than a standard thoracotomy. In the second model, a chronically isolated upper airway lamb preparation was developed. With careful postoperative care, lambs in this group appear to display normal activity along with the absence of any breathing problems.

Overall, the development of these two unique animal models not only represents an important aspect of the present study, but also paves the way for further studies on the interrelationships between upper and lower airways receptors.

In conclusion, we have shown that the increase in inspiratory activity of glottal muscle constrictor, occurring when nasal IPPV is increased, originates from bronchopulmonary receptors. Beyond the overall clinical relevance of this knowledge in the care of newborn infants treated with nPPV, the demonstration of further interrelationships between the lower and upper airways is of significant physiological importance.

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