Effects of Inspiratory Pressure Rise Time and Hypoxic or Hypercapnic Breathing on Inspiratory Laryngeal Constrictor Muscle Activity During Nasal Pressure Support Ventilation

Vincent Carrière, MSc1; Danny Cantin, MSc1; Stéphanie Nault, BSc1; Charlène Nadeau, AHT1; Nathalie Samson, PhD1; Jennifer Beck, PhD2,3; Jean-Paul Praud, MD, PhD1

Objective: We previously reported the development of an active inspiratory laryngeal narrowing against ventilator insufflations when inspiratory pressure is increased during nasal pressure support ventilation in lambs. The present study aimed to further understand the factors involved in this inspiratory laryngeal narrowing.

Methods: This study was funded by an operating grant from the Canadian Institutes of Health Research and the Canada Research Chair in Neonatal Respiratory Physiology allocated to Dr. Praud. Mr. Carrière was supported by a MD-MSc training scholarship from the Fonds de la recherche Québec – Santé (FRQS). Dr. Beck consulted for, received royalties from, and has patents with Maquet Critical Care. She has been reimbursed by Maquet Critical Care (Solna, Sweden) for attending several conferences. She has participated as a speaker in scientific meetings or courses organized and financed by Maquet Critical Care. Through Neurovent Research (NVR), she serves as a consultant to Maquet Critical Care. The following disclosure was agreed upon by University of Toronto, Sunnybrook Health Sciences Centre, St. Michael’s Hospital, and the Research Ethics Boards of Sunnybrook and St. Michael’s to resolve conflicts of interest: Dr. Beck has made inventions related to neural control of mechanical ventilation that are patented. The patents are assigned to the academic institution(s) where inventions were made. The license for these patents belongs to Maquet Critical Care. Future commercial uses of this technology may provide financial benefit to Dr. Beck through royalties. Dr. Beck owns 50% of Neurovent Research Inc (NVR). NVR is a research and development company that builds the equipment and catheters for research studies. NVR has a consulting agreement with Maquet Critical Care. St. Michael’s Hospital has a research agreement with Maquet Critical Care AB (Solna, Sweden) and receives royalty and overhead from this agreement. Dr. Praud is a member of the Sherbrooke University Hospital Research Center, which is funded by the FRQS. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: jean-paul.praud@usherbrooke.ca

Copyright © 2015 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

DOI: 10.1097/CCM.0000000000001080

More specifically, we tested the hypothesis that a short inspiratory pressure rise time or a low Paco2 level promotes inspiratory laryngeal narrowing observed in nasal pressure support ventilation. The effect of hypoxia was also assessed.

Design: Prospective, randomized, interventional study.

Setting: Animal research laboratory at the Faculty of Medicine and Health Sciences, Université de Sherbrooke, Canada.

Subjects: Thirteen lambs aged 4–5 days.

Interventions: Polysomnographic recordings were performed in chronically instrumented lambs to study states of alertness, glottal muscle electrical activity, tracheal pressure, Spo2, and respiratory movements. Lambs were ventilated with progressively increasing levels of nasal pressure support ventilation (10/4, 15/4, and 20/4 cm H2O), using a broad range of inspiratory rise times from 0.05 to 0.4 s. Thereafter, either CO2 (Paco2 = baseline value + 10 mm Hg) or N2 (Paco2 = 45–55 mm Hg) was added to the inspiratory line.

Measurements and Main Results: The percentage of respiratory cycles with phasic inspiratory activity of glottal constrictor muscle was measured and compared between the various experimental conditions. The different inspiratory pressure rise times tested did not alter the phasic inspiratory activity of glottal constrictor muscle during nasal pressure support ventilation. By contrast, this activity was virtually abolished by increasing Paco2 in all lambs. Finally, no alterations in the phasic inspiratory activity of glottal constrictor muscle during nasal pressure support ventilation were observed during hypoxia.

Conclusions: Active inspiratory laryngeal narrowing during nasal pressure support ventilation is not altered by inspiratory rise times ranging from 0.05 to 0.4 s or by moderate hypoxia, whereas a moderate increase in Paco2 abolishes this activity. (Crit Care Med 2015; XX:00–00)

Key Words: active inspiratory laryngeal closure; increase in arterial Paco2; inspiratory rise time; nasal pressure support ventilation

N
oninvasive ventilation (NIV) is increasingly used in children and neonates for treating severe respiratory conditions (1–3). The main purpose of NIV use is
to avoid the severe complications potentially associated with endotracheal intubation, such as ventilator-associated pneumonia, tracheal bleeding, or stenosis (2, 4).

However, whereas endotracheal ventilation delivers gas mixture directly into the trachea, in NIV, the insufflated gas must first travel through the upper airways before reaching the lungs. Clinical relevance of this major difference relates to the previous demonstration in adult humans (5), as well as in lambs (6–8), that increasing pressure levels during NIV can induce an active glottal narrowing during inspiration, responsible for an increased laryngeal resistance to ventilatory insufflations. This increased resistance may promote patient-ventilator asynchrony (9, 10) and lead to alveolar hypoventilation (11), as well as divert the insufflated gas into the digestive system. The latter can be especially harmful in infants, where gastric distension can lead to further respiratory compromise (12).

Understanding the factors involved in inspiratory laryngeal narrowing is thus relevant to prevent such deleterious consequences. Study by the group of Rodenstein et al (11) on volume-controlled NIV showed that high inspiratory flow, sleep, and hypocapnia increased laryngeal resistance. Our studies on nasal pressure support ventilation (nPSV) showed that a minimum level of inspiratory pressure (most often 15 cm H2O) was needed in lambs to observe active inspiratory laryngeal narrowing. Subsequent experiments demonstrated that the latter was at least partly explained by a vagal reflex originating from the subglottal airways (8). Furthermore, we showed that inspiratory laryngeal narrowing was absent during nasal neurally adjusted ventilatory assist (nNAVA), a recent NIV modality designed to be more physiological (6). Interestingly, the progressive rise in insufflation pressure during nNAVA is designed to mimic the slow rise in diaphragm electrical activity throughout inspiration. This is at odds with nPSV, where the inspiratory pressure rise time is much shorter. Such differences between nPSV and nNAVA formed the basis for the first aim of the present study, namely to verify whether the occurrence of inspiratory laryngeal narrowing during nPSV was linked to a short inspiratory pressure rise time.

Hypocapnia is well known as a promoter of active laryngeal closure during the postinspiratory phase of the breathing cycle (= the first part of expiration), as well as during central apneas (13–15). Our previous results on nPSV suggest that, although not mandatory, a low PaCO2 favors inspiratory laryngeal narrowing during nPSV (6). Accordingly, the second aim of this study was to verify the hypothesis that increasing the inspired CO2 concentration reduces the occurrence of inspiratory laryngeal narrowing during nPSV in lambs.

Finally, while the effect of hypoxia on postinspiratory laryngeal muscle activity is unclear (13, 16, 17), its effect on inspiratory glottal activity is, to our knowledge, totally unknown. Due to the frequency of hypoxia in patients supported by NIV, the third aim of this study was to assess the effect of hypoxia on the occurrence of laryngeal narrowing during nPSV in lambs.

MATERIALS AND METHODS

For supplementary details regarding Materials and Methods section, see supplemental data (Supplemental Digital Content 1, http://links.lww.com/CCM/B304).

Animals

Experiments were conducted on a convenience sample of 16 full-term lambs aged 4–5 days. The study was approved by the Ethics Committee for Animal Care and Experimentation of the Université de Sherbrooke. The care and handling of the animals were in accord with the Canadian Council on Animal Care.

Chronic Instrumentation

Surgery was performed under general anesthesia. Electrodes and catheters were inserted to measure electrical activity of the thyroarytenoid (EAta, a glottal constrictor) and cricothyroid (a laryngeal dilator) muscles, arterial blood gases, tracheal end-expiratory CO2, and states of alertness. In addition, respiratory movements (inductance plethysmography) and oxygen hemoglobin saturation (SpO2) were recorded. All signals were transmitted via our custom-designed radio telemetry transmitters and continuously recorded. The lamb was filmed using a webcam and an observer was systematically present to note all events occurring during recordings.

Ventilatory Equipment

nPSV was performed using a SERVO-i Ventilator (Maquet, Solna, Sweden). nPSV was flow-triggered and flow-cycled and administered through a custom-designed plaster nasal mask molded to fit the lamb’s nose (for an illustration of the custom-designed nasal mask for lambs, see Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/CCM/B305).

Design of the Study

Following a 48-hour postoperative recovery period, recordings were performed without sedation. All painful procedures were minimized as much as possible. Similarly, no drugs were used on the experimental day, to avoid any unwanted effect on respiratory function. Each lamb was used as its own control. Two sets of experiments were performed in two different groups of eight lambs. The first set of experiments focused on the effects of 1) short inspiratory pressure rise times, up to the maximum setting available for use in infants and young children in the “Infant” mode of the Servo-i; 2) increasing PaCO2; or 3) decreasing PaO2, within limits of clinical relevance. The second set of experiments further tested the effect of the longest inspiratory pressure rise time available with the Servo-i (0.4 s) to match the rise time observed in nNAVA, where active inspiratory laryngeal narrowing was consistently absent.

First Set of Experiments in Eight Lambs. Effect of inspiratory pressure rise time on inspiratory EAta during nPSV.

In all eight lambs, nPSV was first applied with three different inspiratory pressure rise times, namely 0.1, 0.12, and 0.15 s, used in random order in each lamb. For each inspiratory pressure rise time, a step-by-step increase in ventilation was used. Pressure support levels of 6, 11, and 16 cm H2O above
a positive end-expiratory pressure of 4 cm H₂O (nPSV 10/4, nPSV 15/4, and nPSV 20/4) were used. At least 2 minutes of quiet sleep (QS) were recorded, and arterial blood gases were measured under each pressure level/rise time condition. Given the consistent observation in the first four lambs that altering inspiratory pressure rise times from 0.1 to 0.15 s did not prevent the development of inspiratory EAta, both shorter and longer inspiratory pressure rise times (0.05 and 0.2 s, representing minimal and maximal rise times available for infants) were also assessed in the last four lambs.

Effect of increasing Pco₂ on inspiratory EAta during nPSV. After obtaining baseline PaCO₂ without ventilatory support, nPSV was again administered at 10/4, 15/4, and 20/4 cm H₂O (rise time fixed at 0.12 s) until reaching the level where inspiratory EAta (%inspiEAta) was observed in over 50% of respiratory cycles during QS. Thereafter, while continuing nPSV administration at the same pressure level for the remainder of the experiment, CO₂ was added into the inspiratory line to reach a PaCO₂ of 10 mm Hg (± 2 mm Hg) above baseline PaCO₂. At least 2-minute recordings during QS were obtained when PaCO₂ targets were reached. Finally, CO₂ addition was halted for a final 2-minute recording during QS. Arterial blood gases were analyzed at each step to ensure that PaCO₂ targets were met.

Effect of moderate hypoxia on inspiratory EAta during nPSV. After obtaining baseline PaO₂ without ventilatory support, nPSV was again administered at 10/4, 15/4, and 20/4 cm H₂O (rise time fixed at 0.12 s); arterial blood gases were measured at each step to ensure that PaO₂ targets were met. nPSV level was then reduced to 10/4 cm H₂O before adding N₂ into the inspiratory line. nPSV levels were once again increased step-by-step, while constantly adjusting inspiratory N₂ flow to maintain PaO₂ values between 45 and 55 mm Hg with serial blood gas analyses. Two-minute recordings in QS were obtained at each nPSV level.

Second Set of Experiments in Eight Lambs. In eight additional lambs, nPSV was administered at 10/4, 15/4, and 20/4 with the inspiratory pressure rise time set at 0.10 s; the same sequence was repeated with an inspiratory rise time of 0.4 s.

Data Analysis

States of Alertness. Standard electrophysiological and behavioral criteria were used to recognize periods of QS. If QS was not observed after 10 minutes of recording, the latter was deemed satisfactory when a 2-minute period of quiet wakefulness was obtained.

Respiratory Dependent Variables. The first minute of recording in QS with good quality data was selected for analysis at each nPSV level and/or each Paco₂/Pao₂ condition. Respiratory rate was calculated from the sum signal of the respiratory inductance plethysmography. The %inspiEAta was also calculated as the percentage of respiratory cycles with inspiratory EAta, along with measurement of arterial PaCO₂, PaO₂, and pHa.

Figure 1. Absence of effect of varying the inspiratory rise time (IRT) during nasal pressure support ventilation (nPSV) on the % of respiratory cycles with phasic inspiratory activity of the thyroarytenoid muscle (%inspiEAta): IRT ranging from 0.1 s to 0.15 s at nPSV 10/4, 15/4, and 20/4 cm H₂O in eight lambs (A); assessment of the entire range of IRTs available in the Infant mode of the SERVO-i (from 0.05 to 0.2 s) at nPSV 15/4 cm H₂O in four of the eight lambs (B); assessment of a very long IRT (0.4 s) to match the average IRT observed in nasal neurally adjusted ventilatory assist at nPSV 15/4 cm H₂O in eight additional lambs (C). Boxes represent interquartile ranges (upper = Q3, middle line = median, bottom = Q1), while the whiskers delineate the maximum and minimum value range.
Statistical Analysis
Normality was systematically tested using both the Shapiro-Wilk test and histogram distribution of the data. Data were expressed as mean (sd) for normally distributed variables and as median (Q1, Q3) for not normally distributed variables. Statistical analyses were performed on raw data for all dependent variables. Variables with a normal distribution were analyzed by the one-way repeated-measures analysis of variance (ANOVA), whereas not normally distributed variables were analyzed by the Wilcoxon signed-rank test or the Friedman test as appropriate (for supplementary details regarding the specific test used for each variable, see supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/B304). Differences were considered significant if p value was less than 0.05. When necessary, multiple comparisons were performed using the Tukey range test for one-way repeated-measures ANOVA or post hoc comparison for Friedman test (SPSS statistics 22; IBM Corp., Armonk, NY).

RESULTS
Effect of Inspiratory Pressure Rise Time on Inspiratory EAta During nPSV
Varying the inspiratory pressure rise time from 0.1 to 0.15 s did not significantly alter %inspiEAta (Fig. 1A). Similarly, further decreasing or increasing the inspiratory pressure rise time to 0.05 or 0.2 s did not have any effect in the four lambs tested (Fig. 1B). Overall, Paco2 and Pao2 values were not significantly different between the various inspiratory pressure rise times tested (Table 1).

Alteration of the inspiratory pressure rise time from 0.1 to 0.4 s in eight additional lambs did not significantly alter the %inspiEAta (Fig. 1C). Again, Paco2 and Pao2 values were not significantly different between conditions (Table 1) (for an illustration of %inspiEAta observed with rise times of 0.1 versus 0.4 s in one lamb, see Supplemental Fig. 2, Supplemental Digital Content 3, http://links.lww.com/CCM/B306).

Effect of Increasing Pco2 on Inspiratory EAta During nPSV
Data analysis was successfully performed in six of the eight lambs (two lambs were excluded due to an unexploitable EAta signal). Paco2 measured at the nPSV level where %inspiEAta was over 50% did not significantly differ from baseline Paco2 values. In all six lambs, addition of CO2 into the inspiratory line in order to reach a Paco2 of 50 ± 6 mm Hg (range, 42.5–59.5 mm Hg) virtually abolished inspiratory EAta from 97% (74, 99) to 0% (0, 0) in 39 ± 31 s (range, 15–90 s) (Fig. 2 and Table 2).

Effect of Hypoxia on Inspiratory EAta During nPSV
Addition of N2 into the inspiratory line induced moderate hypoxia with a slight although significant respiratory alkalosis. In the lambs as a whole, no significant alterations in %inspiEAta were observed at any nPSV level with hypoxia.

TABLE 1. Effect of Inspiratory Pressure Rise Time on Arterial Blood Gases During Nasal Pressure Support Ventilation During Quiet Sleep

<table>
<thead>
<tr>
<th>1st part of the experiment</th>
<th>No ventilatory support (n = 8)</th>
<th>nPSV 10/4 (n = 8)</th>
<th>nPSV 15/4 (n = 7)</th>
<th>nPSV 20/4 (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT (s)</td>
<td>0.1</td>
<td>0.12</td>
<td>0.15</td>
<td>0.12</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>37 (35, 39)</td>
<td>38 (35, 38)</td>
<td>36 (34, 39)</td>
<td>35 (33, 36)</td>
</tr>
<tr>
<td>Pao2 (mm Hg)</td>
<td>88 (83, 91)</td>
<td>89 (86, 94)</td>
<td>92 (88, 94)</td>
<td>90 (88, 96)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2nd part of the experiment</th>
<th>No ventilatory support (n = 4)</th>
<th>nPSV 15/4 (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT (s)</td>
<td>0.12 (1st)</td>
<td>0.05</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>37 (36, 38)</td>
<td>40 (38, 41)</td>
</tr>
<tr>
<td>Pao2 (mm Hg)</td>
<td>91 (89, 92)</td>
<td>87 (82, 90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3rd part of the experiment</th>
<th>No ventilatory support (n = 8)</th>
<th>nPSV 15/4 (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT (s)</td>
<td>0.12</td>
<td>0.4</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>40 (36, 47)</td>
<td>38 (35, 42)</td>
</tr>
<tr>
<td>Pao2 (mm Hg)</td>
<td>74 (55, 87)</td>
<td>90 (75, 93)</td>
</tr>
</tbody>
</table>

nPSV 10/4 = nasal pressure support of 10/4 cm H2O, nPSV 15/4 = nasal pressure support of 15/4 cm H2O, nPSV 20/4 = nasal pressure support of 20/4 cm H2O, RT = inspiratory pressure rise time.

1st part of experiment presents results obtained with inspiratory pressure rise times ranging from 0.1 to 0.15 s in the first eight lambs. 2nd part of experiment presents results obtained with further inspiratory pressure rise times available for use in infants (0.05 and 0.2 s) in four of these eight lambs. 3rd part of experiment presents results obtained with inspiratory rise times extended to 0.4 s (in order to match the average inspiratory rise time observed in nasal neurally adjusted ventilatory assist) in eight additional lambs. Values are presented as median (Q1, Q3). For all comparisons, p value was between 0.1 and 0.9.

XXX 2015 • Volume XX • Number XXX

www.ccmjournal.org

Copyright © 2015 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.
Effect of Inspiratory Pressure Rise Time on Inspiratory EAta During nPSV

This study confirms that ventilator insufflations during nPSV can induce a phasic inspiratory electrical activity of the glottal constrictor muscle in lambs, most often observed at nPSV 15/4 cm H2O.

The absence of any observable effect resulting from varying the inspiratory rise time on the occurrence of inspiratory EAta in nPSV is contrary to our initial hypothesis. Our initial premise stemmed from our previous observation that inspiratory glottal narrowing in nPSV is reflexly driven by bronchopulmonary receptors (8), as well as from the results by Parreira et al (11), showing that a high inspiratory flow induced a higher laryngeal resistance in volume-controlled NIV. As demonstrated herein, a short inspiratory rise time is not involved in our healthy lamb model. The additional observation whereby increasing the inspiratory pressure rise time up to 0.4 s (to match the rise time observed in lambs during nNAVA) did not inhibit inspiratory EAta in nPSV strongly suggests that the slowness of inspiratory airway pressurization in itself does not explain the consistent absence of EAta with nNAVA.

Effect of Increasing Pco2 on Inspiratory EAta During nPSV

This study, in agreement with our previous results (6, 7), shows that a decrease in Pao2 is not a prerequisite for the development of inspiratory EAta during nPSV. On the other hand, adding CO2 into the ventilator inspiratory line consistently

during nPSV is not due to a short rise time in inspiratory pressure. In addition, although inspiratory glottal constrictor muscle EMG activity is most often observed in the absence of any decrease in Paco2 during nPSV, our results further show that a moderate increase in Paco2 strongly inhibits this electrical activity. Finally, no consistent alteration in inspiratory glottal constrictor muscle EMG activity was observed in the presence of moderate hypoxia.

DISCUSSION

Results from this study clearly show that glottal constrictor muscle electrical activity developing against ventilator insufflations (Fig. 3, A and B and Table 3). In addition, for any given lamb, apparent alteration in %inspiEAta at one nPSV level was often in the opposite direction at another nPSV level (Fig. 3C), such that there was no overall trend.

TABLE 2. Effect of Increasing Pco2 on Inspiratory Electrical Activity of the Thyroarytenoid and Respiratory Variables During Nasal Pressure Support Ventilation During Quiet Sleep

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Ventilatory Support (n = 6)</th>
<th>nPSV (n = 6)</th>
<th>nPSV + CO2 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paco2 (mm Hg)</td>
<td>38 (5)</td>
<td>37 (4)</td>
<td>50 (6)</td>
</tr>
<tr>
<td>% inspiEAta (%)</td>
<td>0 (0, 0)</td>
<td>97 (74, 99)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>86 (8)</td>
<td>91 (8)</td>
<td>115 (7)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>60 (20)</td>
<td>30 (11)</td>
<td>65 (10)</td>
</tr>
<tr>
<td>pHa</td>
<td>738 (0.05)</td>
<td>741 (0.06)</td>
<td>731 (0.04)</td>
</tr>
<tr>
<td>HCO3 − (mmol/L)</td>
<td>22 (5)</td>
<td>24 (4)</td>
<td>23 (5)</td>
</tr>
</tbody>
</table>

nPSV = nasal pressure support ventilation, nPSV + CO2 = nasal pressure support ventilation with CO2 added to the inspiratory line, %inspiEAta = % of inspiratory electrical activity of the thyroarytenoid muscle.

*Versus no ventilatory support.

†Versus nPSV.

Results are presented as mean (sd) with the exception of % inspiEAta, which is presented as median (Q1, Q3). Normal font exponent: p between 0.05 and 0.1; underlined exponent: p < 0.05. For all other comparisons, p was between 0.4 and 1.
abolished inspiratory EAta. This result extends previous observations by Jounieaux et al (5) during volume-controlled NIV.

The mechanism responsible for the virtual abolition of inspiratory EAta by flowing CO₂ into the airways remains unknown. This may be related to a direct effect of CO₂ on laryngeal (18) or bronchopulmonary (19) receptor activity. Indeed, stimulation of laryngeal CO₂ receptors enhances upper airway dilator muscle activity; however, the effect is generally observed more rapidly (10–15 s) than in the present study (15–90 s). Furthermore, increasing CO₂ in the subglottal airways can alter the activity of both the slowly adapting bronchopulmonary receptors and the C fiber endings (19). However, we recently showed that C fiber endings are not responsible for inspiratory EAta in nPSV (20); in addition, the frequent observation that the EAta burst ceases well before the end of the inspiratory pressure plateau suggests that EAta does not originate from the slowly adapting bronchopulmonary receptors. Hence, EAta in nPSV likely originates from the stimulation of the rapidly adapting receptors, whose activity is not known to be altered by increasing CO₂ in the airways (19). Irrespectively, inhibition of inspiratory EAta via alteration of any bronchopulmonary receptor activity should not require more than 15 s, unlike our present observation. Finally, given that hypercapnia increases glottal dilator muscle inspiratory activity (21), we propose that increased PaCO₂ likely acts at the level of arterial and/or central chemoreceptors to inhibit inspiratory EAta during nPSV. Notwithstanding the exact mechanism, decreasing inspiratory glottal resistance (= no inspiratory EAta) appears beneficial when PaCO₂ is increased.

Effect of Hypoxia on Inspiratory EAta During nPSV

Review of the literature reveals that the overall effects of hypoxia on postinspiratory thyroarytenoid muscle EMG are unclear, which may be due to variable experimental conditions and/or species-related differences (13, 16, 17). Our previous studies in awake, nonsedated lambs revealed a consistent abolition of postinspiratory EAta during hypoxia in the first weeks of life. Results from these studies suggest that abolition of EAta by hypoxia primarily originates from stimulation of peripheral chemoreceptors (14, 17). However, to the best of our knowledge, this is the first instance in which the controlling influences of inspiratory EAta are studied, and in which, the overall effect of hypoxia on EAta may be different during inspiration and the postinspiratory phase of expiration. Furthermore, for any given lamb, the apparent alteration in inspiratory EAta at one nPSV level was often in the opposite direction at another nPSV level such that there was no overriding trend. Overall, in striking difference with hypercapnia, mild-to-moderate hypoxia had no consistent effect on inspiratory EAta observed during nPSV.

Clinical Relevance

Our present observations, which need to be validated in humans, may have very significant consequences for managing patients during nPSV. According to our results, when adverse consequences of active inspiratory glottal closure are suspected, altering the inspiratory pressure rise time does not appear to be of any benefit. Similarly, correcting any hypoxia would not have consistent results on inspiratory active glottal closure. Conversely, allowing moderate hypercapnia can be expected to have a beneficial effect on the deleterious consequences of active inspiratory glottal closure, the latter of which
Results are presented as median (Q1, Q3) with the exception of pH, which is presented as mean (sd).

Limitations of the Study
The healthy, full-term lambs involved in this study are not meant to be a model of preterm newborns with respiratory distress syndrome. Rather, lambs aged a few days may be a better model of young infants beyond the immediate neonatal period. Irrespectively, the previous observation of active glottal closure during NIV in adult humans, especially during hypocapnia (5), suggests that our results are relevant to humans, from the young infant to the adult.

Given that permissive hypercapnia is now strongly advocated for the treatment of acute respiratory failure (22), one may argue that our observation favoring moderate hypercapnia is no longer relevant. In fact, although permissive hypercapnia is nowadays most often targeted at all ages, hypocapnia is not uniformly achieved in daily practice (23, 24).

Due to the numerous conditions assessed in our study, results were obtained on very short periods of nPSV; furthermore, we only studied healthy lambs. Notwithstanding their remarkable consistency, our observations nonetheless need to be replicated during prolonged nPSV periods and in lambs with acute respiratory failure.

The nasal mask used in this study was very efficient in preventing air leaks. In contrast, unintentional air leaks around the edge of the interface can be significant and very variable during NIV, especially in infants. Our results could potentially have been different in the presence of significant leaks.

Of note, even in the absence of air leaks, we did not encounter significant gastric dilatation, which is a problem encountered in some infants. Such dilatation could also alter the present results.

Given that sedation or analgesia was not used during the recordings to prevent potential interferences with the respiratory drive, light pain and discomfort, especially related to the nasal mask, may have been present. This is similar to human subjects under nasal ventilation. However, pain and discomfort were likely minimal, given that 1) lambs easily fell asleep and 2) measurements were performed during QS.

Finally, although this study may be underpowered due the low number of lambs involved, our results clearly suggest that moderate hypercapnia is at minimum much more efficient in preventing inspiratory glottal closure than (even greatly) increasing inspiratory pressure rise time.

In conclusion, this study shows that moderate hypercapnia abolishes the inspiratory glottal closure developing against ventilator insufflations during nPSV in healthy lambs. Conversely, increasing the inspiratory rise time failed to alleviate this glottal closure. Our results suggest that active inspiratory glottal closure during nPSV can be prevented by moderate permissive hypercapnia.

ACKNOWLEDGMENTS

We thank Mr. Modou Séné, staff biostatistician at the Sherbrooke University Hospital Research Center, for helping in conducting the statistical analyses. The Servo-i ventilator was on loan from Maquet Getinge Group without compensation.

REFERENCES


**TABLE 3. Effect of Hypoxia on Inspiratory Electrical Activity of the Thyroarytenoid and Respiratory Variables During Nasal Pressure Support Ventilation During Quiet Sleep**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Ventilatory Support (n = 7)</th>
<th>nPSV 10/4 (n = 5)</th>
<th>nPSV 15/4 (n = 7)</th>
<th>nPSV 20/4 (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normoxia</td>
<td>Hypoxia</td>
<td>Normoxia</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Pao₂ (mm Hg)</td>
<td>88 (84, 89)</td>
<td>92 (89, 98)</td>
<td>49 (46, 50)</td>
<td>93 (89, 99)</td>
</tr>
<tr>
<td>%inspiEAta (%)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>95 (61, 100)</td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td>35 (34, 38)</td>
<td>36 (35, 37)</td>
<td>33 (31, 33)</td>
<td>36 (34, 37)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>43 (37, 47)</td>
<td>38 (33, 44)</td>
<td>35 (34, 46)</td>
<td>29 (22, 33)</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>21 (20, 24)</td>
<td>21 (20, 23)</td>
<td>22 (21, 22)</td>
<td>22 (20, 25)</td>
</tr>
<tr>
<td>pH</td>
<td>7.39 (0.04)</td>
<td>7.39 (0.04)</td>
<td>7.43 (0.04)</td>
<td>7.41 (0.04)</td>
</tr>
</tbody>
</table>

nPSV = nasal pressure support ventilation, %inspiEAta = % of inspiratory electrical activity of the thyroarytenoid muscle.

*pVersus normoxia at the same nPSV level.

**sd**


