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Effects of nasal continuous positive-airway pressure on nutritive swallowing in lambs

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Bernier A, Catelin C, Ahmed MA, Samson N, Bonneau P, Praud JP. Effects of nasal continuous positive-airway pressure on nutritive swallowing in lambs. J Appl Physiol 112: 1984–1991, 2012. First published April 12, 2012; doi:10.1152/japplphysiol.01559.2011.—Current knowledge suggests that, to be successful, oral feeding in preterm infants should be initiated as soon as possible, often at an age where immature respiration still requires ventilatory support in the form of nasal continuous positive airway pressure (nCPAP). While some neonatologist teams claim great success with initiation of oral feeding in immature infants with nCPAP, others strictly wait for this ventilatory support to be no longer necessary before any attempt at oral feeding, fearing laryngeal penetration and tracheal aspiration. Therefore, the aim of the present study was to provide a first assessment of the effect of various levels of nCPAP on bottle-feeding in a neonatal ovine model, including feeding safety, feeding efficiency, and nutritive swallowing-breathing coordination. Eight lambs born at term were surgically instrumented 48 h after birth to collect recordings of electrical activity of laryngeal constrictor muscle, electrocardiography, and arterial blood gases. Two days after surgery, lambs were bottle-fed under five randomized nCPAP conditions, including without any nCPAP or nasal mask and nCPAP of 0, 4, 7, and 10 cmH2O. Results revealed that application of nCPAP in the full-term lamb had no deleterious effect on feeding safety and efficiency or on nutritive swallowing-breathing coordination. The present study provides a first and unique insight on the effect of nCPAP on oral feeding, demonstrating its safety in newborn lambs born at term. These results open the way for further research in preterm lambs to better mimic the problems encountered in neonatology.

Newborn; bottle-feeding; nutritive swallowing-breathing interaction; laryngeal chemoreflexes

FEEDING DIFFICULTIES represent one of the most worrisome problems in preterm infants (1, 3). Preterm oral feeding is a complex developmental skill. Feeding readiness depends on neurological maturation, severity of illness, and prefeeding autonomic, motor, and behavioral state organization (39, 42). Overall neural immaturity, as well as various disorders frequently encountered in preterm infants such as neurological, digestive, and respiratory problems, is often responsible for delaying feeding maturation and consequently extending hospital length of stay. In addition, the multiple aversive oral and/or nasal procedures such as suctioning of oronasal secretions, insertion and retrieval of nasogastric tube, and endotracheal or nasal ventilatory support, which are used several times a day in preterm infants, often lead to hypersensitivity of the facial area and interfere with feeding maturation (1). Not infrequently, orofacial hypersensitivity leads to feeding problems for years (3, 40).

Various strategies have been developed in an attempt to enhance the acquisition of feeding skills and prevent the above difficulties in premature infants. Nonnutritive sucking has been shown to accelerate transition from tube to bottle-feeding and better bottle-feeding performance (25). Early introduction of oral feeding has also been reported to accelerate feeding maturation (24, 35). Hence, very early development of oral motor competence has been observed with initiation of breastfeeding between 29 and 33 wk of postmenstrual age, full breastfeeding being reached at a postmenstrual age as low as 32 wk (23).

However, preterm infants are often dependent on nasal continuous positive airway pressure (nCPAP) for several weeks after birth (17). A number of neonatology teams refuse to initiate oral feeding in infants while on nCPAP (23), fearing laryngotracheal penetrations and pulmonary aspirations of milk with the consequent potentially deleterious cardiorespiratory events (27, 37, 38). On the other hand, some neonatologists defend the introduction of oral feeding in preterm infants while on nCPAP, as soon as cardiorespiratory stability is present (4, 6). To our knowledge, a detailed assessment of the effect of nCPAP on oral feeding in the neonatal period is not available. The aim of the present study was to provide a first assessment of the effect of various levels of nCPAP on bottle-feeding in a neonatal ovine model, including feeding safety (i.e., presence of cardiorespiratory events), efficiency, and nutritive swallowing-breathing coordination.

MATERIAL AND METHODS

Animals

A total of eight mixed-bred lambs were included in the study. All lambs were born at term by spontaneous vaginal delivery at our local provider’s farm and arrived in our animal quarters 1–2 days after birth. The study protocol was approved by the ethics committee for animal care and experimentation of our institution.

Surgical Preparation

Aseptic surgery was performed in all lambs 2–3 days after birth under general anesthesia (2% isoflurane-30% N2O-68% O2). Anesthesia was preceded by an intramuscular injection of ketamine (10 mg/kg), atropine sulfate (0.1 mg/kg), morphine (0.016 ml/kg), and antibiotics (5 mg/kg gentamicin and 50 mg ampicillin) and an intravenous bolus of Ringer’s lactate solution (10 ml/kg). One dose of ketoprofen (3 mg/kg) was also injected intramuscularly for analgesia and repeated if needed on the next day. Lambs were mechanically ventilated through an orotracheal tube (4.5 mm) during the surgical procedure. Heart rate, rectal temperature, pulse oximetry, end-tidal
Experimental Equipment

Ventricular Equipment. Nasal continuous positive airway pressure (nCPAP) was induced using the Infant Flow nCPAP system (Cardinal Health, Dublin, OH) with heated, humidified air. A nasal mask custom-made from a plaster shell filled with dental paste (to reduce dead space as much as possible) was installed on the lamb’s muzzle to deliver nCPAP, in such a manner that the lamb was able to open its mouth at will and drink from a bottle (34).

Recording equipment. Lamb instrumentation was completed immediately before recordings. A pulse oximeter probe (Masimo Radical, Irvine, CA) was attached at the base of the tail for continuous monitoring of oxygen hemoglobin saturation by pulse oximetry (SpO₂). Arterial blood gases and pH were also measured (IL 1306; Instrumentation Laboratory, Lexington, MA) and corrected for rectal temperature of the lamb (2). In addition, elastic bands for respiratory inductance plethysmography (Respitrace, NIMS, Miami Beach, FL) were installed on the thorax and abdomen to monitor respiratory movements and assess lung volume variations qualitatively. Finally, nCPAP values were continuously monitored from the nasal mask (RX104A pressure transducer, Biopac Systems, Goleta, CA). All recordings were performed in awake lambs, using our custom-designed radiotelemetry system (32). All leads from each electrode were thus connected to this radiotelemetry system, to obtain prolonged recordings in nonsedated lambs under the least possible restraining conditions. The raw EMG signals were rectified, integrated, and moving time averaged (100 ms). All parameters were continuously recorded on a PC using AcqKnowledge software (version 4.1; Biopac Systems) and the entire recording period was filmed using a webcam, allowing us to verify the behavioral state of the lamb during data analysis.

Design of the study. All lambs were cared for without their mother upon arrival in our animal quarters, due to specific needs of the study regarding bottle-feeding familiarization. They were placed in a Plexiglas chamber (1.2 m³; in agreement with recommendations by the Canadian Council for Animal Care for sheep housing) with holes to allow for air circulation. A bottle filled with reconstituted ewe’s milk, from which lambs could drink freely, was placed permanently in the chamber.

The study was performed without sedation at least 45 h after surgery and was designed to allow for simultaneous recording of nutritive swallowing (NS) activity, respiratory movements, ECG, and SpO₂ while bottle-feeding under different nCPAP conditions. The lambs were comfortably positioned in a sling with loose restraints. Two experimenters were present throughout the recordings to note lamb behavior.

Five different nCPAP conditions were randomly assessed, namely, no nasal mask; nasal mask only, i.e., no CPAP or breathing tube (nCPAP0); and nCPAP 4, 7, and 10 cmH₂O, respectively. These pressure values were chosen on the basis of those reported in clinical practice (22, 30). In each condition, following a basal recording of 5 min, the lambs were offered a bottle filled with reconstituted ewe’s milk, heated to 39°C. The nipple of the bottle was the same as the one they had drunk from in the Plexiglas chamber. The quantity of milk offered was the same in each condition and was determined from their feeding habits in the previous days. nCPAP conditions were separated from each other by 2 h, during which the lambs were placed in the Plexiglas chamber without milk, to ensure that they were hungry enough for each condition. The first condition of the morning was also preceded by 2 h without milk. In each condition, the bottle was offered to the lambs a maximum of three times, after which the feeding episode was considered finished. Reasons to pause feeding were mainly lamb discomfort/agitation or lamb refusing to drink. Recordings were continued for 10 min after feeding. Blood samples from the arterial catheter were taken before feeding and at 0, 5, and 10 min thereafter. Rectal temperature was also taken before and after feeding. Every effort was made to assess the five nCPAP conditions on the same day.

Data analysis. All signals were carefully observed and analyzed in relation with the time period (before, during, or after feeding) as well as with the nCPAP condition (verified via the mask pressure trace) and the behavioral state of the lamb, which was determined from the video recorded during the experiments.

Cardiorespiratory variables. For each nCPAP condition, baseline values (i.e., prefeeding values) for heart and respiratory rates (respectively, HR and RR) as well as SpO₂ were averaged on a period of 30 s. The 30-s period closest to the feeding episode during which the lambs were calm was chosen. HR, RR, and SpO₂ during and after feeding were also calculated. For during-feeding values, the latter were obtained by averaging the values of three periods of 30 s taken at the beginning, the middle, and the end of the feeding episode. This averaging during the feeding episode was justified by the absence of any significant differences between the three periods in all lambs. Analyses of cardiorespiratory responses during and after feeding were mostly performed as previously described for laryngeal chemoreflex analysis (36). Briefly, the number of HR slowings (defined by a >25% decrease of HR ≥ 33%) and bradycardias (HR slowing lasting >5 s) were noted, and the percentage of time spent in bradycardia was tabulated. The number of apneas (defined as at least 2 missed breaths relative to baseline breathing) and the percentage of time spent in apnea were also noted. Finally, the number of desaturations <90% and <80% and the percentage of time spent with SpO₂ <90% and <80% were calculated.

Swallowing activity. Nutritive swallowing activity was recognized by a brief, high-amplitude TA EMG burst, as previously validated (29). To assess the relation between NS and respiration, NS were assigned to one of five types depending on the respiratory phase preceding and following NS: ee-type (at the transition from inspiration to expiration), ei-type (at the transition from expiration to inspiration), ii-type (at the transition from inspiration to expiration), ie-type (preceded and followed by inspiration) (29), and ap-type (NS occurring during an apnea). Rhythmic stability of feeding was quantified using the coefficient of variation (COV: SD of the mean interval, divided by the mean interval) (12). Swallow-breath (NS-BR) and breath-breath (BR-BR) intervals were measured and their COVs calculated (11). Only NS and breaths occurring during NS runs were used for analysis of rhythms. A NS run was defined as three or more NS with interswallow intervals of ≥2 s (12). Feeding efficiency was also assessed and included volume of milk intake per unit time (milliliters/minute ratio) or per NS (milliliters/NS ratio), NS frequency, percentage of total NS in runs, and COV of NS-NS interval.
of a significant trend, defined as constraints), it was decided to give full consideration to the presence
lambs (related to both the complexity of the ovine model and ethical
problems prevented saturation measurements in two lambs as
lambs were evaluated under every nCPAP condition, technical
day of recordings were included in the study. Although all
is shown in Fig. 1.

\[ \text{RR, HR, and SpO}_2 \text{ are listed in Table 1. Neither nCPAP nor} \]
\[ \text{nor CPAP nor} \text{were analyzed through a general linear model two-way ANOVA for} \]
\[ \text{blood gases in one lamb (see below). Detailed results} \]
\[ \text{were performed using PROC MIXED of SAS software, version 9.1. Results} \]
\[ \text{were analyzed through a one-way ANOVA for repeated} \]
\[ \text{were the nCPAP condition and the NS type. Other data, if normally distributed} \]
\[ \text{were performed using} \text{ECG, electrocardiogram; TA, electrical activity of the thyroid-}
\[ \text{were the nCPAP condition and the NS type. Other data, if normally distributed} \]
\[ \text{were analyzed using a Shapiro-Wilk test.} \]

**RESULTS**

**General Characteristics**

A sample tracing obtained in one lamb in nCPAP 10 cmH\(_2\)O is shown in Fig. 1.

Eight lambs weighing 3.8 kg (SD 0.3) (range 3.2–4.0) on the
day of recordings were included in the study. Although all
lambs were evaluated under every nCPAP condition, technical
problems prevented saturation measurements in two lambs as
well as blood gases in one lamb (see below). Detailed results
for RR, HR, and SpO\(_2\) are listed in Table 1. Neither nCPAP nor
feeding had an effect on SpO\(_2\), while RR was significantly
increased by the four
conditions with nasal mask both before and after feeding
while during feeding only nCPAP10 increased RR significantly.
No significant interaction was found between nCPAP and feeding
for RR (\(P = 0.8\)), HR, and SpO\(_2\) (\(P = 1.0\) for both).

**Cardiorespiratory Events and Arterial Blood Gases**

The effect of nCPAP conditions and feeding on the percentage
of time spent in apnea is shown in Fig. 2. All other
cardiorespiratory responses to nCPAP and feeding are detailed
in Table 2. Blood gases and pH measurements are listed in
Table 3. For all parameters, no significant interaction between
nCPAP and feeding was found (\(P > 0.1\) for all).

**Apneas**

While nCPAP had no significant effect on the frequency and
the percentage of time spent in apnea (\(P = 1.0\) for both),
feeding significantly increased both parameters in almost all
nCPAP levels when compared with before and after feeding
(\(P < 0.0001\) for both; see Table 2 and Fig. 2 for details).

**Bradycardias and HR Slowings**

The electrocardiogram signal could not be analyzed at
nCPAP0 for one lamb, due to technical problems. Overall, only

![Figure 1](https://example.com/figure1.png)

**Table 1. Effects of nCPAP conditions and feeding on cardiorespiratory variables**

<table>
<thead>
<tr>
<th></th>
<th>No Mask</th>
<th>nCPAP0</th>
<th>nCPAP4</th>
<th>nCPAP7</th>
<th>nCPAP10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RR, min(^{-1})</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>35 (10)</td>
<td>37 (11)</td>
<td>34 (6)</td>
<td>32 (9)</td>
<td>36 (9)</td>
</tr>
<tr>
<td>During</td>
<td>41 (13)</td>
<td>39 (7)</td>
<td>33 (6)*</td>
<td>34 (8)*</td>
<td>38 (6)</td>
</tr>
<tr>
<td>After</td>
<td>45 (11)</td>
<td>37 (9)*</td>
<td>37 (8)*</td>
<td>38 (8)*</td>
<td>36 (7)*</td>
</tr>
<tr>
<td><strong>HR, min(^{-1})</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>168 (25)</td>
<td>201 (31)*</td>
<td>199 (27)*</td>
<td>211 (31)*</td>
<td>221 (38)*</td>
</tr>
<tr>
<td>During</td>
<td>164 (24)</td>
<td>183 (23)*</td>
<td>180 (24)*</td>
<td>184 (22)*</td>
<td>205 (32)*</td>
</tr>
<tr>
<td>After</td>
<td>180 (25)</td>
<td>208 (30)*</td>
<td>206 (32)*</td>
<td>225 (31)*</td>
<td>240 (24)*</td>
</tr>
<tr>
<td><strong>SpO(_2), %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>99 (1)</td>
<td>98 (2)</td>
<td>98 (2)</td>
<td>97 (2)</td>
<td>98 (2)</td>
</tr>
<tr>
<td>During</td>
<td>97 (2)</td>
<td>97 (3)</td>
<td>97 (2)</td>
<td>96 (3)</td>
<td>98 (1)</td>
</tr>
<tr>
<td>After</td>
<td>98 (2)</td>
<td>97 (2)</td>
<td>98 (1)</td>
<td>96 (3)</td>
<td>98 (2)</td>
</tr>
</tbody>
</table>

Values are expressed as means (SD). nCPAP, nasal continuous positive-airway pressure; nCPAP0, nCPAP4, nCPAP7, nCPAP10 refers to nCPAP of 0, 4, 7, and 10 cmH\(_2\)O; RR, respiratory rate; HR, heart rate; SpO\(_2\), hemoglobin O\(_2\) saturation before; before, before feeding; during, during feeding; after, after feeding. *: vs. no mask; #: vs. before; †: vs. nCPAP10; ‡: vs. after; §: vs. nCPAP7. Underlined symbols indicate \(P < 0.05\); normal font symbols indicate \(P \leq 0.1\). All other \(P\) values are \(>0.1\).
one bradycardia (i.e., lasting >5 s) was found. It occurred during feeding in nCPAP7, lasted 10.7 s, and was not associated with any apnea or desaturation. Therefore, statistical analyses were performed only for HR slowings (i.e., lasting >5 s). There was no significant change in the frequency of HR slowings between all nCPAP levels (P = 0.8). However, the frequency of HR slowings was significantly increased during feeding compared with before and after, both in the no mask and nCPAP0 conditions (see Table 2 for details). Since not clinically relevant, the duration of HR slowings was not analyzed.

**Arterial Blood Desaturations**

Due to technical problems with the pulse oximeter probe in two lambs, saturation could only be analyzed in six of the eight lambs. SpO2 fell below 80% only once, during feeding in nCPAP7 before feeding, and was not associated with any apnea or bradycardia. Therefore, statistical analyses were performed only for SpO2 < 90%. There was no significant change in the frequency of desaturations between all nCPAP levels (P = 0.5). However, the percentage of time spent with SpO2 < 90% was increased in nCPAP7 compared with no mask and nCPAP4 during feeding (P = 0.1 for both) and compared with nCPAP4 after feeding (P = 0.1). Feeding significantly increased the frequency of desaturations in nCPAP0 compared with before and after feeding (P = 0.01 and 0.05, respectively), but had no effect on the percentage of time spent with SpO2 < 90% (P = 0.5).

**Arterial Blood Gases and pH**

Due to technical problems with the arterial catheter in one lamb, arterial blood gases and pH could only be measured in three of the eight lambs.

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**Table 2. Effects of nCPAP conditions and feeding on cardiorespiratory events**

<table>
<thead>
<tr>
<th></th>
<th>No mask</th>
<th>nCPAP0</th>
<th>nCPAP4</th>
<th>nCPAP7</th>
<th>nCPAP10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apnea frequency</strong>, min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.1 (0.2)†</td>
<td>0.2 (0.2)</td>
<td>0.1 (0.2)</td>
<td>0.1 (0.2)</td>
<td>0.2 (0.3)</td>
</tr>
<tr>
<td>Feeding</td>
<td>0.7 (0.7)*†</td>
<td>0.5 (0.6)*†</td>
<td>0.7 (0.7)*†</td>
<td>0.6 (0.5)*†</td>
<td>0.5 (0.5)*†</td>
</tr>
<tr>
<td>After</td>
<td>0.03 (0.05)†</td>
<td>0.04 (0.1)†</td>
<td>0.1 (0.2)†</td>
<td>0.05 (0.1)†</td>
<td>0.05 (0.1)†</td>
</tr>
<tr>
<td><strong>HR slowing frequency</strong>, min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.1 (0.1)</td>
<td>0.2 (0.3)</td>
<td>0.05 (0.1)</td>
<td>0.1 (0.2)</td>
<td>0.4 (0.7)</td>
</tr>
<tr>
<td>Feeding</td>
<td>3 (5)*†</td>
<td>2 (3)*†</td>
<td>2 (3)†</td>
<td>4 (7)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>After</td>
<td>0.4 (0.9)</td>
<td>0.1 (0.1)</td>
<td>0.1 (0.2)</td>
<td>0.2 (0.3)</td>
<td>0.2 (0.3)</td>
</tr>
<tr>
<td><strong>Desaturation frequency</strong>, min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.1 (0.2)</td>
<td>0.03 (0.08)</td>
</tr>
<tr>
<td>Feeding</td>
<td>0.04 (0.1)</td>
<td>0.4 (0.7)*†</td>
<td>0.1 (0.3)</td>
<td>0.2 (0.4)</td>
<td>0.1 (0.2)</td>
</tr>
<tr>
<td>After</td>
<td>0.03 (0.05)</td>
<td>0.1 (0.1)</td>
<td>0</td>
<td>0.1 (0.2)</td>
<td>0.02 (0.04)</td>
</tr>
<tr>
<td>%Time spent in desaturation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (9)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Feeding</td>
<td>1 (3)*‡</td>
<td>5 (9)</td>
<td>1 (3)*‡</td>
<td>7 (17)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>After</td>
<td>1 (3)</td>
<td>4 (6)</td>
<td>0*‡</td>
<td>6 (9)</td>
<td>0.2 (0.5)</td>
</tr>
</tbody>
</table>

Values are expressed as means (SD). †: vs. after; *: vs. before; ‡: vs. nCPAP7. Underlined symbols indicate P < 0.05, normal font symbols indicate P ≤ 0.1. All other P values are >0.1. See Table 1 for abbreviations.
seven lambs. There was a significant decrease in pH in nCPAP7 and nCPAP10 when compared with nCPAP0 before feeding (P < 0.05 for both). Similarly, 10 min after feeding, pH was significantly decreased by nCPAP10 compared with nCPAP0 (P < 0.1). However, mean pH always remained within physiological limits (see Table 3). No significant effect of nCPAP was observed on either PaO2 or PaCO2 (P > 0.5 and 0.9, respectively). Feeding had no effect on either pH, PaO2, or PaCO2 (P > 0.6, 1.0, and 0.2, respectively).

In summary, nCPAP had no systematic effect on cardiopulmonary responses and blood gases. Similarly, feeding had no clear effect on all variables with the exception of apneas, for which feeding systematically increased frequency and percentage of time spent in apnea.

Feeding Efficiency

The effects of nCPAP on feeding efficiency are listed in Table 4 and illustrated in Fig. 3. There were no significant changes in total NS frequency and percentage of total NS in runs for all nCPAP levels (P > 0.6 and 0.2, respectively). Similarly, the stability of NS rhythm (COV of NS-NS interval) and the milliliters/minute ratio were not disturbed in any nCPAP level (P > 0.9 and 0.3, respectively). Nevertheless, when compared with every other condition, nCPAP10 significantly decreased the milliliters/NS ratio (see Fig. 3, middle, for details).

In summary, nCPAP had no effect on feeding efficiency except for a significant decrease of the milliliters/NS ratio by nCPAP10 when compared with all the other conditions.

Coordination Between Nutritive Swallowing and Phases of the Respiratory Cycle

The effects of nCPAP on NS-BR coordination are reported in Table 4 and Fig. 4. Overall, NS-BR coordination was similar for all conditions. The COV of NS-BR interval did not differ between nCPAP levels (P = 0.9) and neither did the COV of BR-BR interval (P = 0.4). Similarly, no statistical differences were observed when the percentage of each NS type was compared among all nCPAP conditions (P = 1.0). Distribution of NS types was similar between conditions, with ii-, ie-, and

### Table 3. Effects of nCPAP conditions and feeding on arterial blood gases and pH

<table>
<thead>
<tr>
<th></th>
<th>No Mask</th>
<th>nCPAP0</th>
<th>nCPAP4</th>
<th>nCPAP7</th>
<th>nCPAP10</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2, Torr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>85 (12)</td>
<td>92 (11)</td>
<td>93 (12)</td>
<td>91 (4)</td>
<td>88 (9)</td>
</tr>
<tr>
<td>0 after</td>
<td>87 (17)</td>
<td>89 (10)</td>
<td>91 (10)</td>
<td>88 (19)</td>
<td>92 (8)</td>
</tr>
<tr>
<td>5 after</td>
<td>86 (18)</td>
<td>89 (12)</td>
<td>89 (15)</td>
<td>88 (19)</td>
<td>91 (8)</td>
</tr>
<tr>
<td>10 after</td>
<td>84 (15)</td>
<td>91 (17)</td>
<td>90 (13)</td>
<td>88 (13)</td>
<td>93 (11)</td>
</tr>
<tr>
<td>PaCO2, Torr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>43 (3)</td>
<td>43 (4)</td>
<td>42 (2)</td>
<td>43 (2)</td>
<td>43 (5)</td>
</tr>
<tr>
<td>0 after</td>
<td>40 (5)</td>
<td>40 (5)</td>
<td>41 (3)</td>
<td>42 (2)</td>
<td>42 (4)</td>
</tr>
<tr>
<td>5 after</td>
<td>42 (4)</td>
<td>41 (4)</td>
<td>42 (2)</td>
<td>41 (3)</td>
<td>41 (5)</td>
</tr>
<tr>
<td>10 after</td>
<td>42 (3)</td>
<td>42 (3)</td>
<td>40 (2)</td>
<td>40 (3)</td>
<td>42 (7)</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>7.44 (0.05)</td>
<td>7.45 (0.04)</td>
<td>7.42 (0.04)</td>
<td>7.41 (0.02)*</td>
<td>7.41 (0.03)*</td>
</tr>
<tr>
<td>0 after</td>
<td>7.41 (0.02)</td>
<td>7.42 (0.02)</td>
<td>7.41 (0.04)</td>
<td>7.41 (0.02)</td>
<td>7.41 (0.03)</td>
</tr>
<tr>
<td>5 after</td>
<td>7.43 (0.03)</td>
<td>7.43 (0.03)</td>
<td>7.41 (0.04)</td>
<td>7.41 (0.02)</td>
<td>7.41 (0.03)</td>
</tr>
<tr>
<td>10 after</td>
<td>7.43 (0.04)</td>
<td>7.43 (0.02)</td>
<td>7.41 (0.04)</td>
<td>7.42 (0.02)</td>
<td>7.41 (0.03)*</td>
</tr>
</tbody>
</table>

Values are expressed as means (SD). Before, before feeding; 0 after, immediately after feeding; 5 after, 5 min after feeding; 10 after, 10 min after feeding. *: vs. nCPAP0. Underlined symbols indicate P < 0.05, normal font symbols indicate P ≤ 0.1. All other P values are >0.1.

### Table 4. Effects of nCPAP conditions on feeding efficiency and nutritive swallowing-breathing coordination

<table>
<thead>
<tr>
<th></th>
<th>No Mask</th>
<th>nCPAP0</th>
<th>nCPAP4</th>
<th>nCPAP7</th>
<th>nCPAP10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding efficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of NS in runs</td>
<td>96 (6)</td>
<td>86 (19)</td>
<td>93 (7)</td>
<td>93 (13)</td>
<td>97 (3)</td>
</tr>
<tr>
<td>COV NS-NS</td>
<td>0.5 (0.1)</td>
<td>0.5 (0.1)</td>
<td>0.4 (0.1)</td>
<td>0.5 (0.05)</td>
<td>0.5 (0.1)</td>
</tr>
<tr>
<td>Nutritive swallowing-breathing coordination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COV NS-BR</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.1)</td>
<td>0.7 (0.1)</td>
<td>0.7 (0.1)</td>
</tr>
<tr>
<td>COV BR-BR</td>
<td>0.5 (0.2)</td>
<td>0.4 (0.2)</td>
<td>0.5 (0.2)</td>
<td>0.5 (0.3)</td>
<td>0.4 (0.1)</td>
</tr>
</tbody>
</table>

Values are expressed as means (SD). NS, nutritive swallowing; COV NS-NS, coefficient of variation of NS-NS intervals; COV NS-BR, COV of NS-breath intervals; COV BR-BR, COV of BR-BR intervals. All P values are >0.1.

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ei-type NS significantly more frequent than both ee- and ap-type NS in almost all conditions (see Fig. 4).

In summary, nCPAP had no significant effect on NS-BR coordination. In addition, although some NS types were more frequent than others, NS could occur at any moment in the respiratory cycle.

**DISCUSSION**

**Statement of Principal Findings**

The present study provides a first and unique insight on the effects of nasal continuous positive airway pressure on bottle-feeding in the newborn full-term lamb. Overall, our findings reveal that application of nCPAP in the full-term lamb has no deleterious effects on both the safety and efficiency of bottle-feeding, aside from a decreased efficiency with the highest nCPAP value (nCPAP10). In addition, our results show that nutritive-breathing coordination is not altered by nCPAP.

**Safety of Bottle-Feeding During nCPAP**

Nasal CPAP has been previously reported to induce dilatation of laryngeal opening in preterm infants (9). On this basis, several neonatology teams are reluctant to initiate oral feeding in infants receiving nCPAP (23), probably fearing the cardiorespiratory consequences of triggering laryngeal chemoreflexes due to increased laryngeal penetration of milk. On one hand, previous results from our laboratory showing severe cardiorespiratory events in preterm lambs during laryngeal chemoreflexes triggered by milk during spontaneous room air breathing may be seen as giving support to these fears (37). On the other hand however, very recent unpublished observations by our group in preterm lambs that nCPAP (6 cmH2O) efficiently prevents these severe events justify further studies aiming at delineating the conditions where feeding can be attempted in newborns with nCPAP.

In the present study, both the frequency and the percentage of time spent in apnea were significantly increased during feeding compared with the prefeeding baseline period in every experimental condition, including the no mask condition. This result is not surprising given that apneas due to bursts of NS are frequently observed both in term and preterm infants (13, 15, 16), owing to the normal inhibition of the respiratory central pattern generator (CPG) induced by NS (19). Moreover, the fact that there was no significant change in blood gases/pH, apneas, or HR slowing when comparing all five conditions suggests that the application of nCPAP itself did not cause any increase in laryngeal penetrations or tracheal aspirations. The slight, albeit significant, increase in percentage of time spent with SpO2/H1102190% during nCPAP7 might be interpreted, in the absence of any increase in apnea, as due to a decreased tidal volume. However, such interpretation appears unlikely since nCPAP10 had no such effect.

The observation of an increased HR with the nasal mask is also noticeable. The presence of an increase in all mask conditions compared with the no mask condition suggests that it may be related to behavioral influence via increased sympathetic tone or to trigeminal stimulation, as reported in term infants (41). Previous results from our laboratory showing no difference in HR between nCPAP6 and nCPAP0 support the fact that the nasal mask itself is mostly responsible for the increase in HR in the present study (31). However, the significant increase in HR during feeding in nCPAP10 may be due to a sympathetic response to decreased venous return at this high nCPAP level, in an effort to maintain a normal cardiac flow (18). Nevertheless, the effects of the application of the mask and nCPAP were overall of little importance since they did not affect cardiorespiratory events.

**Feeding Efficiency During nCPAP**

Various clinical conditions, such as postmenstrual age (21), intrauterine drug exposure (11), bronchopulmonary dysplasia (10), and acute viral bronchiolitis of infancy (26), have been shown to affect feeding efficiency, as measured by either the milliliters/NS ratio, percentage of total NS in runs, NS fre-
quency, or COV of NS-NS interval. However, results of the present study indicate that nCPAP has no effect on feeding efficiency. The only notable exception is the application of nCPAP 10 cmH2O, which significantly decreased the milliliters/NS ratio and appeared to have a similar although nonsignificant effect on the milliliters/minute ratio.

Previous studies from our group showed an inhibiting effect of nCPAP on nonnutritive swallowing (NNS) in newborn lambs during quiet sleep, mediated by stimulation of both bronchopulmonary and upper airway receptors (33, 34). In addition, continuous lung inflation prompted by application of negative extrathoracic pressure in awake adult humans was also shown to inhibit water-triggered swallows (14). In the present study, NS frequency was not significantly altered under any nCPAP condition. We are unable to explain at this time the apparent discrepancy between the two above-quoted studies and the present study.

Overall, nCPAP 10 cmH2O was the only condition to have a slight deleterious effect on feeding efficiency, a fact that has however little clinical impact since this level of nCPAP is rarely used in neonates (30).

Effect of nCPAP on Nutritive Swallowing-Breathing Coordination

Nutritive swallowing-breathing coordination is crucial for minimizing the risk of aspiration and the consequent deleterious cardiorespiratory events. Our previous studies (33, 34) revealed that nCPAP had no systematic effect on NNS-breathing coordination in full-term lambs. Similarly, the present study indicates that nCPAP has no effect on NS-breathing coordination in full-term lambs. Overall, the coordination of breathing and NNS as well as NS appears to be largely unaltered by various conditions such as preterm birth (28), hypoxia (8), nCPAP, and nasal intermittent positive-pressure ventilation (33, 34). Furthermore, the present results suggest that stimulation of positive pressure receptors in the upper airways by nCPAP, in likelihood with upper airway dilation, do not significantly alter NS in the neonatal period, including NS-breathing coordination. Finally, it appears that the nCPAP-associated stimulation of bronchopulmonary receptors, especially stretch receptors, probably together with an increased functional residual capacity, do not significantly alter NS in the neonatal period, including NS-breathing coordination.

Clinical Implications and Limitations of our Study

Our observation in the present study that clinically relevant levels of nCPAP do not have deleterious consequences on the safety and efficacy of bottle-feeding, as well as on swallowing-breathing coordination, may be considered reassuring for those advocating for initiation of oral feeding despite the presence of nCPAP (4, 6). Moreover, we used a custom-made nasal mask, which is clearly heavier and more cumbersome than the nasal interfaces currently in use in human newborns. However, our results are obviously limited by the fact they were obtained in the healthy, full-term lamb. Different results might be obtained in preterm sick human infants, since prematurity and altered lung function tend to interfere with normal control of feeding (7, 20). Therefore, our present observations have to be considered as a first, albeit necessary, step toward the acquisition of a better knowledge of the relationships between nCPAP and oral feeding in the neonatal period. Further experiments will need to address the effect of nCPAP in preterm lambs, including with respiratory problems mimicking bronchopulmonary dysplasia, before contemplating a knowledge transfer to a clinical trial in the neonatal intensive care unit.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: A.B., C.C., N.S., and J.-P.P. conception and design of research; A.B., M.A.H.-A., and N.S. performed experiments; A.B., N.S., and P.B. analyzed data; A.B., C.C., and J.-P.P. interpreted results of experiments; A.B. prepared figures; A.B. drafted manuscript; C.C. and N.S. edited and revised manuscript; J.-P.P. approved final version of manuscript.

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