Absence of inspiratory laryngeal constrictor muscle activity during nasal neurally adjusted ventilatory assist in newborn lambs

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Hadj-Ahmed MA, Samson N, Bussières M, Beck J, Praud JP. Absence of inspiratory laryngeal constrictor muscle activity during nasal neurally adjusted ventilatory assist in newborn lambs. J Appl Physiol 113: 63–70, 2012. First published April 19, 2012; doi:10.1152/japplphysiol.01496.2011.—In nonsedated newborn lambs, nasal pressure support ventilation (nPSV) can lead to an active glottal closure in early inspiration, which can limit lung ventilation and divert air into the digestive system, with potentially deleterious consequences. During volume control ventilation (nVC), glottal closure is delayed to the end of inspiration, suggesting that it is reflexly linked to the maximum value of inspiratory pressure. Accordingly, the aim of the present study was to test whether inspiratory glottal closure develops at the end of inspiration during nasal neurally adjusted ventilatory assist (nNAVA), an increasingly used ventilatory mode where maximal pressure is also reached at the end of inspiration. Polysomnographic recordings were performed in eight nonsedated, chronically instrumented lambs, which were ventilated with progressively increasing levels of nPSV and nNAVA in random order. States of alertness, diaphragm, and glottal muscle electrical activity, tracheal pressure, Spo2, tracheal PetCO2, and respiratory inductive plethysmography were continuously recorded. Although phasic inspiratory glottal constrictor electrical activity appeared during nPSV in 5 of 8 lambs, it was never observed at any nNAVA level in any lamb, even at maximal achievable nNAVA levels. In addition, a decrease in PCO2 was neither necessary nor sufficient for the development of inspiratory glottal constrictor activity. In conclusion, nNAVA does not induce active inspiratory glottal closure, in contrast to nPSV and nVC. We hypothesize that this absence of inspiratory activity is related to the more physiological airway pressurization during nNAVA, which tightly follows diaphragm electrical activity throughout inspiration.

nasal intermittent positive pressure ventilation; diaphragm electrical activity; pressure support ventilation; thyroarytenoid muscle; quiet sleep

Nasal intermittent positive pressure ventilation (nIPPV) is increasingly used for treating acute respiratory distress in lieu of endotracheal IPPV, including in infants (24). The use of nIPPV is aimed at preventing the severe complications related to the presence of an endotracheal tube, such as pulmonary infections, tracheal bleeding, tracheal granuloma, and subglottic stenosis (24, 29). Common indications for nIPPV in infants include weaning from endotracheal ventilation, as well as the treatment of respiratory distress syndrome, chronic lung disease, severe apneas of prematurity, and respiratory syncytial virus infection (3, 15, 20, 24, 32).

However, an important difference using a nasal interface as opposed to an endotracheal tube for mechanical ventilation is the interposition of the laryngeal valve between the ventilator and the lungs. Recently, we showed that increasing the level of nIPPV in newborn lambs induces an active laryngeal narrowing during inspiration with increased laryngeal resistance opposing ventilator insufflations (25). The potential clinical importance of these observations is related to the fact that active laryngeal narrowing can restrict lung ventilation and divert air towards the digestive system during insufflation, a particular concern in the infant, who is thereby exposed to gastric distension and further respiratory compromise (17, 22). By using our unique ovine models with either upper airways separated from the lower airways or intrathoracic vagotomy, we were able to show that this inspiratory laryngeal narrowing was at least partly explained by a vagal reflex originating from the subglottal airways (34).

Our previous results on nIPPV were obtained with both volume-controlled ventilation (VC) and pressure support ventilation (PSV). One intriguing difference between these two ventilatory modes is that although inspiratory thyroarytenoid muscle electrical activity (EAta; a glottal constrictor muscle) was observed immediately at the onset of inspiration in PSV and returned to zero before the end of inspiration, its occurrence was delayed to the end of inspiration in VC, suggesting that EAta was reflexly linked to peak inspiratory pressure via stimulation of bronchopulmonary receptors. Were this hypothesis correct, it should also hold true with other ventilatory modes where insufflation pressure peaks at the end of inspiration, such as in neurally adjusted ventilatory assist (NAVA). In recent years, the use of NAVA has been rapidly expanding in intensive care units because of its many perceived advantages and its unique paradigm (11, 14, 28). Of particular interest is the fact that during NAVA, insufflation pressure is driven by the level of electrical activity of the diaphragm (EAdi), tightly following the progressive increase in EAdi throughout each inspiration (37) and peaking at the end of inspiration. Hence, in an attempt to further elucidate the mechanisms responsible for active laryngeal narrowing during nasal IPPV, the primary aim of the present study was to verify whether inspiratory EAta is also present at the end of inspiration during nasal NAVA.

Second, several studies reported an enhancement of EAta by hypocapnia, especially during the postinspiratory phase of the breathing cycle and during central apneas (19, 30, 40). Thus hypocapnia may be another mechanism contributing to inspiratory laryngeal narrowing during nIPPV. Interestingly, NAVA

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offers the opportunity to further test this hypothesis. Indeed, the obligatory dependence of the insufflation pressure on EAdi level ensures a tailored inspiratory support during NAVA, such that, theoretically, over-assist and hypocapnia cannot develop. Taking advantage of this peculiarity of NAVA, the secondary aim of this study was to test whether inspiratory laryngeal narrowing can develop in the absence of hypocapnia. Because of the need to record glottal muscle electrical activity intramuscularly, hence precluding study in human infants, the study was performed in our unique newborn ovine model.

MATERIAL AND METHODS

Animals

Experiments were conducted in eight mixed-bred term lambs aged from 4 to 9 days and weighing 4.2 kg (SD 0.8; range 2.66–5.52 kg). The study was approved by the ethics committee for animal care and experimentation of the Université de Sherbrooke. All lambs were housed with their mother in our animal quarters.

Surgical Instrumentation

Aseptic surgery was performed in all lambs at 2 days of life, under general anesthesia (1–2% isoflurane + 30% N2O + balance O2), after an intramuscular injection of atropine sulfate (0.1 mg/kg), ketamine (10 mg/kg), and morphine (25 µg/kg) and an intravenous bolus (10 ml/kg) of Ringer lactate solution. One dose of ketoprofen (3 mg/kg) was also injected intramuscularly if needed, based on a combination of clinical signs (tachycardia and/or tachypnea, flopping ears, decreased activity and/or appetite). Antibiotics (5 mg/kg gentamicin and 0.05 ml/kg duplocilline) were administered intramuscularly prior to surgery and daily thereafter. Chronic instrumentation was performed as described previously (12). Briefly, custom-made bipolar gold electrodes were inserted into both thyroarytenoid muscles (a laryngeal constrictor) and cricothyroid muscles (a laryngeal dilator) for EAta and EAct recordings. Two needle electrodes were inserted into the parietal cortex directly through the skull for electrocorticogram (ECoG), with a third needle electrode inserted under the scalp as a ground. Two custom-made silver electrodes were inserted subcutaneously close to the right eye socket for electrooculogram (EOG) recordings. A catheter was inserted into the right carotid artery for blood sampling and gas analysis. In addition, two custom-made catheters were installed between the third and fourth and the fifth and sixth tracheal rings to record tracheal pressure and end tidal CO2 (PetCO2). Finally, a 20-Fr voice prosthesis (Blom-Singer Advantage, InHealth Technologies, Carpinteria, CA) was placed between the cervical esophagus and the skin to allow a one-way access to the esophagus to insert a catheter for recording EAdi (see below). Postoperative care included daily temperature and weight monitoring, as well as daily flush of the arterial catheter with heparin solution. Lambs were euthanized at the end of experiments by pentobarbital overdose. Correct electrodes positioning was systematically verified at necropsy.

Recording Equipment

Polysomnographic recordings (Fig. 1) were obtained by using our custom-built radiotelemetry system with channels for ECoG, EOG, and muscle EA (23). The raw signals were sampled at 1,000 Hz, rectified, and moving-time averaged at 100 ms. Thoracic and abdominal volume variations were qualitatively assessed using respiratory inductance plethysmography (Ambulatory Monitoring, Ardsley, NY). A pulse oximeter sensor (LNOP Y1 reflectance sensor, Masimo, Irvine, CA) was attached at the base of the tail for continuous monitoring of arterial hemoglobin saturation (SpO2) and pulse wave. Mask pressure (Pmask; a measure of the level of ventilator support) and tracheal pressure (Ptrach; a measure of the ventilator support reaching the lower airways) were continuously recorded using two pressure transducers (TSD160A, Biopac Systems, Santa Barbara, CA). PetCO2 was recorded using a CO2 analyzer (Capnogard, model 1265, Respironics).

An 8-Fr NAVA catheter was inserted into the esophagus through the voice prosthesis until the voice output decreased to the level of the crural diaphragm as...
which resulted in a peak inspiratory pressure close to 10 cmH2O, i.e.,
as follows. NAVA
waveform. As described previously (10), three time cursors were
generated for each breath on the displayed EAdi waveform: 1) onset of
inspiratory EAdi signal, 2) peak of EAdi, and 3) onset of next
inspiratory EAdi signal. The period from onset to peak EAdi signal
was identified as the neural inspiratory time and used to calculate
the peak phasic EAdi during inspiration. The period from peak EAdi
to the onset of the next inspiratory EAdi signal was identified as the
neural expiration time. Neural respiratory rate was calculated using
the above identified neural inspiratory and expiratory times. The
EAdi-time product (an indication of diaphragm energy expenditure)
was calculated per minute as the product of the mean inspiratory
phasic EAdi, the neural inspiratory time, and the neural respiratory
rate (10). Values were averaged for 60 s.

The percentage of respiratory cycles with inspiratory phasic EAta
(%inspirEAta) was calculated. In addition, the mean amplitude of
phasic inspiratory EAta (ampliEAta) was determined and expressed in
proportion to the maximum EAta amplitude (averaged during 4
swallows in each lamb). Similarly, the percentage of respiratory
cycles with phasic inspiratory EAct (%inspirEAct) was calculated, as
even as the mean amplitude of phasic inspiratory EAct (ampliEAct),
expressed in proportion to the averaged EAct during CPAP 0
recordings. Finally, PETCO2 was measured during the last minute of
the recording at each ventilatory level. Paco2, Paco2, and pH were mea-
sured on arterial blood sampled at the end of each ventilatory level.

Statistical Analysis
All variables (RR, VT, PETCO2, Paco2, Paco2, pH, EAdi-time product,
%inspirEAta, ampliEAta, %inspirEAct, ampliEAct) were expressed as
mean (SD). Statistical analyses were performed on raw data for all
variables. Normality was first systematically tested using the Shapiro-
Wilk test and histogram distribution of the data. The first set of
analyses tested the effect of the mode and level of ventilation (inde-
dependent variables). Blood gases, respiratory rate, and PETCO2 (normal
distribution) were analyzed through a general linear model two-way
ANOVA for repeated measures using PROC MIXED of SAS soft-
ware (version 9.1.3). The remaining variables, namely pH, VT, EAdi-
time product, %inspirEAta and %inspirEAct, ampliEAta, and ampliEAct
(not normally distributed) were analyzed with Friedman’s test fol-
lowed by the post hoc Wilcoxon signed rank test using SPSS (SPSS
statistics 17.0). Second, a regression analysis was performed to test
the relationship between %inspirEAta or ampliEAta and Paco2 or
PETCO2 using PROC GENMOD of SAS. Differences were considered
significant if P < 0.05. In addition, given the relatively small number
of studied lambs, a P < 0.1, indicative of a tendency toward a
significant difference, was fully considered in the discussion of the
results.

RESULTS
Experiments were completed in 8 newborn term lambs
without sedation (age: 5 ± 2 days; weight: 4.2 ± 0.9 kg).
Examples of recordings obtained for muscle activities at PSV
20/4 and NAVA max and for pressures applied from CPAP 0
to PSV 20/4 and to NAVA max are given in Figs. 2 and 3,
respectively.

Ventilatory Variables
A progressive decrease in RR was observed with increasing
nPSV as well as nNAVA level (Table 1). Overall, a 44% and
38% decrease in RR was observed respectively with PSV 20/4
(P = 0.0002) and NAVA max (P = 0.001) compared with
CPAP 4. RR at PSV 20/4 was not different from RR at NAVA
max. Simultaneously, VT increased with both nPSV and
nNAVA (Fig. 4), the value observed with nNAVA max being
comparable to the value observed with nPSV 15/4.
Although arterial blood gas values could be obtained in 7 of 8 lambs studied, PETCO2 was recorded in all 8 lambs (Table 1). Overall, a significant decrease in both PaCO2 ($P < 0.02$) and PETCO2 ($P < 0.0001$) was progressively observed with increasing levels of PSV. Simultaneously, a tendency toward a decrease in PETCO2 was only observed between CPAP 4 and NAVA max ($P = 0.06$). In addition, both PaCO2 ($P = 0.04$) and PETCO2 ($P = 0.0007$) were significantly lower at PSV 20/4 than NAVA max. An overall significant increase in pH ($P = 0.03$) was only observed in PSV. Finally, no significant changes in PaO2 were observed with either increasing PSV or NAVA modes.

A significant decrease in EAdi-time product was observed with increasing nNAVA level ($P = 0.02$). With increasing PSV level, the EAdi-time product decreased significantly at both PSV 15/4 ($P = 0.04$) and PSV 20/4 ($P = 0.05$) compared with CPAP 4. In addition, EAdi-time product tended to be lower at PSV 20/4 than at NAVA max ($P = 0.08$; Fig. 4).

**Inspiratory Active Laryngeal Closure During Nasal Ventilation**

Overall, although phasic inspiratory EAta (glottal constrictor activity) appeared with increasing PSV in 5 of 8 lambs, it was never observed at any NAVA level (Fig. 2). In PSV, phasic inspiratory EAta was observed in 2 of 8 lambs from PSV 10/4 upwards, in 2 additional (total of 4) lambs from PSV 15/4 and in an additional lamb (total of 5) with PSV 20/4 (Table 2). In addition, in the 5 lambs with phasic inspiratory EAta during nPSV, %inspirEAta increased in proportion with PSV level ($P = 0.02$; Fig. 5A). Regression analysis showed a positive relationship between the increase in %inspirEAta and ampliEAct ($P = 0.008$). The presence of phasic inspiratory EAta in PSV was also associated with a significantly higher difference $[P_{mask} - P_{trach}]$ for maximum values of inspiratory pressure ($P < 0.0001$, Wilcoxon signed-rank test; see Fig. 6). Simultaneously, both %inspirEAct and ampliEAct dramatically de-

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**Fig. 2.** Electrical activity (EA) of thyroarytenoid (ta; a glottal constrictor), cricothyroid (ct; a glottal dilator) and diaphragm (di) muscle during nasal pressure support ventilation (PSV) and neurally adjusted ventilatory assist (NAVA) during quiet sleep in 1 lamb. Contrary to NAVA max, PSV 20/4 triggers inspiratory EAta. EAta, thyroarytenoid muscle EA; fEAta, moving time averaged EAta; EAct, cricothyroid muscle EMG; fEAct, moving time averaged EAct; Pmask, mask pressure; Vlung, lung volume variations, given by the sum signal of respiratory inductance plethysmography (inspiration upwards); I, inspiration; e, expiration.

**Fig. 3.** Variations of Pmask during: PSV (10/4, 15/4 and 20/4 cmH2O) (A) and NAVA (NAVA 1, NAVA 2 and NAVA max) (B) mode in 1 lamb. Contrary to PSV, breath-by-breath variations of Pmask were observed at all NAVA levels, reaching a highly irregular pattern at NAVA max. Such a high irregularity would not be appropriate in clinical practice, this level being assessed in the present experiment to study the highest possible peak inspiratory pressures in NAVA.
increased with application of CPAP 4, then virtually disappeared in 7 lambs with increasing nPSV (Fig. 5B).

**Relationship Between Inspiratory Glottal Constrictor Muscle Activity and Decrease in PCO2 during nPSV**

In the 5 lambs with presence of phasic inspiratory EAta in nPSV, regression analysis showed a significant relationship between the decrease in PetCO2 or PaCO2 and the increase in %InspirEAta (P = 0.009 and P = 0.1, respectively). However, as shown in table 2, a decrease in PaCO2 was neither necessary (lamb 7) nor sufficient (lamb 3) for the development of phasic inspiratory EAta in nPSV. In addition, the development of hypocapnia in nNAVA (lamb 6) was not accompanied by the development of phasic inspiratory EAta.

**DISCUSSION**

This study demonstrates for the first time the effect of increasing nasal NAVA levels on laryngeal constrictor and dilator muscle activity in nonsedated, newborn lambs. In contrast to nasal pressure support ventilation, we observed that nasal NAVA does not induce active laryngeal constrictor inspiratory EMG in any lamb, even at maximal achievable NAVA level. In addition, our results show that hypocapnia is neither necessary nor sufficient for the development of active NAVA level. In contrast to nasal pressure support ventilation, we observed that PetCO2, mmHg increased with application of CPAP 4, then virtually disappeared in 7 lambs with increasing nPSV (Fig. 5B).

**Thyroarytenoid and Cricothyroid Electrical Activity During nPSV and nNAVA in Quiet Sleep**

The present study confirms that increasing the level of nasal PSV can induce phasic inspiratory EMG activity of a glottal constrictor muscle in lambs, whereas phasic inspiratory EMG activity of a glottal dilator muscle virtually disappears, in agreement with results from our two previous studies (25, 34). The observation of lower inspiratory PIP values compared with Pmask when inspiratory EAta is present in PSV is also in agreement with our previous study in inspiratory upper airway resistance when phasic inspiratory EAta is present during nIPPV (24) as well as with laryngoscopic observations in human adults of glottal narrowing when nIPPV level is increased (27). Of particular note, the present results confirm that inspiratory glottal narrowing can occur even with low-pressure level nPSV (10/4 cmH2O) in some lambs (25). As alluded to in the Introduction, such consequences of nPSV on upper airway resistance are important to know, as they could contribute to difficulties in patient-ventilator interaction, as underlined in a recent review (31). Hence, by increasing laryngeal resistance, active glottal narrowing developing against ventilator insufflations could be responsible for oral leaks or complications related to diversion of insufflated air into the digestive system, which is of special concern in the newborn (17, 22). On the contrary, the total absence of any
phasic inspiratory EAta during nNAVA, including at maximal achievable NAVA level, is noteworthy and clearly at variance with nPSV. This absence of inspiratory EAta may partly explain the observed improvement in ventilator-patient interaction, which was recently reported in infants and children with nNAVA compared with nPSV (1, 13, 39).

Potential Explanations for the Absence of Inspiratory Glottal Constrictor EMG in nNAVA and Its Presence in nPSV

During nPSV, insufflation from the ventilator is performed with a constant level of pressure and time course set by the clinician, often with a short inspiratory rise time to further decrease the patient’s inspiratory work (26). The consequent rapid airway pressurization at the onset of inspiration could be responsible for triggering, in a reflex manner, the inspiratory EMG activity of the glottal constrictor muscles, which are mediated by vagal reflexes originating from below the larynx (34). On the other hand, during nNAVA, the ventilator is driven by the respiratory centers, the amplitude, and time course pattern of the insufflation varying from breath to breath, closely following EAdi. In other words, under central drive, airway pressurization at onset of inspiration is always progressive in nNAVA, such that the pressure rise mimics the normal progressive recruitment of the diaphragmatic motor units (9). In this respect, future studies will undoubtedly need to question the importance of the inspiratory rise time in the development of inspiratory glottal constrictor muscle activity during nPSV. Of note, tidal volume in itself does not appear to be involved in the active glottal narrowing observed with nPSV. Indeed, despite a similar Vt value (Fig. 4), phasic inspiratory EAta was

Table 2. Percentage of respiratory cycles with inspiratory phasic activity of the thyroarytenoid muscle and PaCO2 during nasal pressure support ventilation or NAVA in lambs during quiet sleep

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<tr>
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<th>Nasal Pressure Support Ventilation</th>
<th>Nasal NAVA</th>
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<tr>
<td></td>
<td>10/4</td>
<td>15/4</td>
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<tr>
<td></td>
<td>%inspirEAta</td>
<td>PaCO2</td>
</tr>
<tr>
<td>Lamb 1</td>
<td>0</td>
<td>—</td>
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<tr>
<td>Lamb 2</td>
<td>51</td>
<td>40.5</td>
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<tr>
<td>Lamb 3</td>
<td>0</td>
<td>53.5</td>
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<td>Lamb 4</td>
<td>0</td>
<td>38</td>
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<tr>
<td>Lamb 5</td>
<td>17</td>
<td>55</td>
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<tr>
<td>Lamb 6</td>
<td>0</td>
<td>35</td>
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<tr>
<td>Lamb 7</td>
<td>0</td>
<td>40.5</td>
</tr>
<tr>
<td>Lamb 8</td>
<td>0</td>
<td>45.5</td>
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%inspirEAta: percentage of ventilatory cycles with EAta.

Fig. 5. Glottal constrictor (EAta) and dilator (EAct) muscle activity during the increase in nPSV and nNAVA. A: percentage of ventilatory cycles with EAta (%inspirEAta) and amplitude of EAta (ampliEAta) are given for the 5 lambs with EAta in nPSV. AmpliEAta is given in percentage of maximal recorded EAta during recording (i.e., during a swallow). B: percentage of ventilatory cycles with EAct (%inspirEAct) and amplitude of EAct (ampliEAct) are given for all 8 lambs. AmpliEAct is given in percentage of phasic inspiratory EAct recorded while on CPAP 0.
present in half of the lambs at PSV 15/4 but in none of the lambs at NAVA max. Coupled with our previous results (34), this observation suggests that rapidly adapting bronchopulmonary receptors, which are more sensitive to rapid change in pulmonary volume (6), are more likely to be responsible for inspiratory glottal narrowing than slowly adapting bronchopulmonary receptors during nPSV.

However, rapid pressurization is not the unique mechanism responsible for inspiratory EAta during nIPPV, as shown by the observation of delayed EAta until the end of inspiration in nVC, after a progressive increase in insufflation pressure throughout inspiration (25). The absence of inspiratory EAta in nNAVA, despite maximal inspiratory pressures roughly identical to nVC (25), shows that the maximal positive pressure value reached during inspiration is not the crucial factor responsible for active laryngeal narrowing. Although unclear, the absence of the latter appears to be related in some manner to the more physiological pressurization of the airways in NAVA, which directly depends on the preset central drive, from the onset of and throughout inspiration.

Enhancement of glottal constrictor muscle EMG activity by hypcapnia has been reported by several studies, especially during the postinspiratory phase of the breathing cycle and during central apneas (19, 30, 40). Certain measurements in our previous studies, however, suggested that the development of inspiratory EAta with increasing nIPPV was not related to a decrease in PCO₂ (25). In the present study, where PCO₂ variations were accurately monitored, the significant relationship between the decrease in PCO₂ and the increase in EAta (in the 5 lambs with EAta) suggests that the decrease in PCO₂ is involved in the development of inspiratory EAta during nPSV. However, as a whole, our present results show that a decrease in PCO₂ is neither necessary nor sufficient for the development of inspiratory EAta during nIPPV. The present findings are in agreement with previous suggestions that CO₂ level is only partly responsible for glottal narrowing under nIPPV and that mechanical factors (pressure, flow) probably also influence glottal behavior (27). Future studies using application of various PCO₂ levels, from hypcapnia to hypercapnia, will be needed to further delineate the potential importance of PCO₂ level in the development of inspiratory glottal constrictor muscle EMG during nPSV.

In conclusion, the observation that nNAVA does not induce inspiratory glottal constrictor muscle activity in nonsedated newborn lambs, even at maximal achievable levels, appears as a further advantage compared with the widely used nPSV. Although this can be of immediate clinical consequence for addressing inadequate patient-ventilator synchronization and the potential relevance of shifting from nPSV to nNAVA in such conditions, further studies are nevertheless necessary to explore the physiological reasons behind this clear difference brought about by nNAVA.

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DISCLOSURES

Dr. Beck has made inventions related to neural control of mechanical ventilation that are patented. 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.