ABSENCE OF INSPIRATORY LARYNGEAL CONSTRICTOR MUSCLE ACTIVITY DURING NASAL NEURALLY ADJUSTED VENTILATORY ASSIST IN NEWBORN LAMBS

Mohamed Amine Hadj-Ahmed[†], Nathalie Samson[†], Jennifer Beck*, Jean-Paul Praud[†]

[†] Neonatal Respiratory Research Unit, Departments of Pediatrics and Physiology, Université de Sherbrooke, QC, Canada, J1H 5N4

* Keenan Research Centre in the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, M5B 1W8 Canada and Department of Pediatrics, University of Toronto, Canada

Short title: Laryngeal closure and neurally adjusted ventilator assist

Address for correspondence and proofs:
Jean-Paul Praud MD PhD
Departments of Pediatrics and Physiology
Université de Sherbrooke
J1H 5N4, QC Canada
Tel: (819) 346-1110, ext 14851
Fax: (819) 564-5215
email: Jean-Paul.Praud@Usherbrooke.ca

ABSTRACT

It has been demonstrated that a progressive increase in nasal pressure support ventilation (nPSV) leads to an active inspiratory glottal closure in non-sedated newborn lambs, which limits lung ventilation (24, 33). Unlike nPSV, the pressure delivered during nasal Neurally Adjusted Ventilatory Assist (nNAVA) is synchronized to the diaphragm electrical activity on inspiration (36). Given the tight neural integration of the glottal dilators and constrictors with diaphragm activity on inspiration and expiration respectively, the aim of the present study was to test the hypothesis that inspiratory glottal closure does not develop during nNAVA. Polysomnographic recordings were performed in eight non-sedated, 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, SpO_2, tracheal $P_{ET}CO_2$ and respiratory inductive plethysmography were continuously recorded. While phasic inspiratory glottal constrictor electrical activity appeared with increasing levels of nPSV in 5 out 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 arterial PCO_2 was neither necessary nor sufficient for the development of phasic inspiratory glottal constrictor activity. In conclusion, nNAVA does not induce active glottal closure in non-sedated newborn lambs at high-pressure levels, in contrast to nPSV.

KEYWORDS: Nasal intermittent positive pressure ventilation, diaphragm electrical activity, pressure support ventilation, thyroarytenoid muscle, glottis, quiet sleep.

INTRODUCTION

Nasal intermittent positive pressure ventilation (nIPPV) is increasingly used for treating acute respiratory distress in lieu of endotracheal IPPV, including in infants (23). 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 (23, 28). Common indications for nIPPV in infants include respiratory distress syndrome, weaning from endotracheal ventilation, treatment of chronic lung disease, severe apneas of prematurity and respiratory syncytial virus infection (3, 15, 19, 23, 31).

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 have shown that increasing the level of nIPPV in newborn lambs induces an active laryngeal narrowing during inspiration with increased laryngeal resistance opposing ventilator insufflations (24). Further experiments showed that this reflex laryngeal narrowing mainly originates from the lower airways and is vagally mediated (33). The potential clinical importance of these observations is related to the fact that active laryngeal narrowing restricts lung ventilation and diverts air towards the digestive system during insufflation, thereby exposing the infant to gastric distension and further respiratory compromise (16, 21).

Our previous results on nIPPV were obtained both with volume-controlled ventilation and pressure support ventilation (PSV). Despite the fact that these modes are routinely used for both invasive and non-invasive ventilation in intensive care units, major asynchronies

between the ventilator and the patient can occur, both in terms of the timing and level of assist provided (1, 10, 11, 13, 14, 27).

Neurally-adjusted ventilatory assist (NAVA) largely overcomes difficulties encountered with the usual assisted ventilation modes by providing a more physiological ventilatory assistance to patients (36). This is mainly because of its unique paradigm, where the electrical activity (EA) of the diaphragm (EAdi) triggers and cycles off the ventilator, thereby improving patient-ventilator interaction (1, 10, 11, 13, 14, 27). In addition, the automatic adaptation of the strength of the insufflation upon the level of EAdi throughout each inspiration in NAVA ensures a tailored inspiratory support (36). Thus, down-regulation of the EAdi with increasing assist prevents over-assist by the ventilator, and studies have shown that, unlike PSV, it is not possible to hyperventilate with NAVA to the point of diaphragm inactivity (20). Also, when used for non-invasive ventilation, the neural trigger used during nNAVA is largely unaffected by leaks, contrary to all other non-invasive ventilation modes, including PSV, which are flow- or pressure-triggered (8, 9). Finally, the close neural integration between the timing of upper airway dilators and diaphragm inspiratory EA (17, 35), together with NAVA's unique characteristics, make this mode an attractive option, especially for nasal, non-invasive ventilation, including in the newborn.

The main objective of this study was to test the hypothesis that the more physiological approach taken to assist ventilation in nNAVA prevents the development of inspiratory activity of laryngeal constrictor muscle, contrary to nPSV, in non-sedated, chronically instrumented newborn lambs. In addition, because over-assist and hypocapnia are much more likely to develop with nPSV than nNAVA, a secondary aim of the study was

to test whether hypocapnia is involved in the development of inspiratory laryngeal narrowing observed in PSV.

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 % N_2O + balance O_2), 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's lactate solution. One dose of ketoprofen (3 mg/kg) was also injected intramuscularly for analgesia and repeated if needed 12h later. 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 (ta, a laryngeal constrictor) and cricothyroid muscles (ct, 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 in order to record tracheal pressure and end tidal CO_2 ($PetCO_2$). Finally, a 20 Fr voice prosthesis (Blom-Singer Advantage, InHealth Technologies, Carpinteria, CA, USA) was placed between the cervical esophagus and the skin to allow a one-way access to the esophagus in order to insert a catheter for recording EAdi (see below). Post-operative 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 (figure 1) were obtained by using our custom-built radiotelemetry system with channels for ECoG, EOG and muscle EA (22). The raw signals were sampled at 1000 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, USA). Airflow was collected using a pneumotachograph (21070B + 47304A flow transducer, Hewlett Packard, Palo Alto, CA, USA) attached to the nasal mask. A pulse oximeter sensor (LNOP YI reflectance sensor, Masimo, Irvine, CA, USA) was attached at the base of the tail for continuous monitoring of arterial hemoglobin saturation (SpO_2) 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, USA). $PetCO_2$ was recorded using a CO_2 analyzer (Capnogard®, Model 1265, Respironics, Inc., California, USA).

An 8Fr “NAVA catheter” was inserted into the esophagus through the voice prosthesis down to the level of the crural diaphragm as previously described (4, 8). This catheter contains an array of miniaturized sensors for measurement of the EAdi waveform (2). A dedicated window for verifying electrode positioning was consulted throughout the protocol (7).

All parameters were continuously recorded using AcqKnowledge software (version 4.1, Biopac Systems, Santa Barbara, CA, USA). In addition, an observer was continuously present to note all events occurring during recordings. Finally, arterial blood gases were determined using a blood gas analyzer (GEM Premier 3000 PAK, Instrumentation Laboratory, Lexington, MA, USA) and systematically corrected for rectal temperature of the lamb (5).

Ventilatory equipment

Nasal pressure support ventilation (nPSV) and neurally-adjusted ventilatory assist (nNAVA) were performed using a Servo-*i* Ventilator (Maquet Critical Care®, Solna, Sweden) with heated (33ºC) and humidified air. Nasal PSV was triggered by flow. The muzzle of each lamb was fitted with a nasal mask custom-built from a plaster shell filled with dental paste, as previously described (34).

Design of study

All lambs were housed with their mother in our animal quarters until the experimental day. Following a postoperative recovery period of 48 hours, polysomnographic recordings were performed without sedation, while lambs were comfortably positioned in a sling with loose restraints. Following a first recording with the nasal mask only (i.e. no ventilatory support), a nasal CPAP of 4 cmH_2O was applied for the second recording. Nasal PSV and NAVA were then tested in all lambs in random order, while maintaining a positive end expiratory pressure (PEEP) at 4 cmH_2O. In the PSV mode, three different levels of pressure support were successively studied, namely 6, 11 and 16 cmH_2O (= peak inspiratory pressure of 10, 15 and 20 cmH_2O) (24, 33). In the NAVA mode, 3 levels, arbitrarily called NAVA levels 1 and 2 and NAVA max, were determined in each lamb as follows. NAVA level 1 corresponded to the proportionality factor, which resulted in a peak inspiratory pressure close to 10 cmH_2O, i.e., matching the first PSV level. Similarly, NAVA level 2 corresponded to a peak inspiratory pressure close to 15 cmH_2O, while NAVA max was the maximum achievable level of NAVA in the lamb under study. We aimed at recording at least 5 minutes of quiet sleep (QS) for each condition (Baseline, CPAP, all nPSV levels and all nNAVA levels). The potential involvement of hypocapnia in the development of active glottal closure with nPSV or nNAVA during QS was assessed as follows. First, $PetCO_2$ was measured from the dedicated tracheal sampling catheter. Because of technical constraints (condensation in the sampling catheter after more than 1-min recording), $PetCO_2$ was recorded during the last minute

of each ventilatory level. In addition, $PaCO_2$, PaO_2 and pH were measured on arterial blood sampled at the end of each ventilatory level.

Data analysis

States of alertness: Standard electrophysiological and behavioral criteria were used to recognize QS from wakefulness and active sleep (32). Only periods of established QS were analyzed.

Respiratory variables

At each ventilatory level, the first 60 seconds of continuous QS were selected for analysis. Respiratory rate (RR) was calculated from the airflow wave obtained with the pneumotachograph, as well as from the mask pressure and the sum signal of the respiratory inductance plethysmography. Expiratory tidal volume (V_T, ml/kg) was measured by integration of airflow using a Hewlett-Packard 21070–60040 pneumotachograph interposed between the ventilator and nasal mask.

In addition, breath-by-breath analysis was performed on the EAdi waveform. As described previously (10), three time cursors were placed for each breath on the displayed EAdi waveform: (i) onset of inspiratory EAdi signal, (ii) peak of EAdi, and (iii) 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 seconds.

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 well as the mean amplitude of phasic inspiratory EAct (ampliEAct), expressed in proportion to the averaged EAct during CPAP 0 recording. Finally, $PetCO_2$ was measured during the last minute of the recording at each ventilatory level. PaCO2, PaO2 and pH were measured on arterial blood sampled at the end of each ventilatory level.

Statistical analysis

All variables (RR, V_T, $PetCO_2$, $PaCO_2$, PaO_2, 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 (independent variables). Blood gases, respiratory rate and $PetCO_2$ (normal distribution) were analyzed through a general linear model two-way ANOVA for repeated measures using PROC MIXED of SAS software (version 9.1.3). The remaining variables, namely pH, V_T, EAdi-time product, %inspirEAta and %inspirEAct, ampliEAta and ampliEAct (not normally distributed) were analyzed with Friedman's test followed by the post-hoc Wilcoxon

signed rank test using SPSS (SPSS statistics 17.0). Secondly, a regression analysis was performed to test the relationship between %inspirEAta or ampliEAta and $PaCO_2$ or $PetCO_2$ 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 towards 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 figures 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 ($P = 0.001$), as compared to CPAP 4. RR at PSV 20/4 was not different from RR at NAVA max. Simultaneously, V_T increased with both nPSV and nNAVA (figure 4), the value observed with nNAVA max being comparable to the value observed with nPSV 15/4.

While arterial blood gas values could be obtained in 7 of 8 lambs studied, $PetCO_2$ was recorded in all 8 lambs (Table 1). Overall, a significant decrease in both $PaCO_2$ ($P = 0.02$) and $PetCO_2$ ($P < 0.0001$) was progressively observed with increasing levels of PSV. Simultaneously, a tendency towards a decrease in $PetCO_2$ was only observed between CPAP 4 and NAVA max ($P = 0.06$). In addition, both $PaCO_2$ ($P = 0.04$) and $PetCO_2$ ($P = 0.0007$) 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 PaO_2 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 to CPAP 4. In addition, EAdi-time product tended to be lower at PSV 20/4 than at NAVA max ($p = 0.08$) (figure 4).

Inspiratory active laryngeal closure during nasal ventilation

Overall, while phasic inspiratory EAta (glottal constrictor activity) appeared with increasing PSV in 5 of 8 lambs, it was never observed at any NAVA level (figure 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 ($P = 0.02$) (figure 5A). Regression analysis showed a positive relationship between the increase in %inspirEAta and ampliEAta ($p = 0.008$). Though not formally quantified, the presence of phasic inspiratory EAta in PSV was associated with a higher difference between Pmask and Ptrach (figure 6). Simultaneously, both %inspirEAct and ampliEAct dramatically decreased with application of CPAP 4, then virtually disappeared in 7 lambs with increasing nPSV (figure 5).

Relationship between inspiratory glottal constrictor muscle activity and decrease in PCO_2 during nPSV

In the 5 lambs with presence of phasic inspiratory EAta in nPSV, regression analysis showed a significant relationship between the decrease in $PetCO_2$ or $PaCO_2$ and the increase in %inspirEAta ($p = 0.009$ and $p = 0.1$, respectively). However, as shown in table 2, a decrease in PCO_2 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 non-sedated, 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 glottal closure with nasal pressure support ventilation.

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 2 previous studies (24, 33). The qualitative observation of lower inspiratory Ptrach values compared to Pmask is also in agreement with our previously reported increase 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 (26). Of particular note, the present results confirm that inspiratory glottal narrowing can occur with clinically relevant, low level nPSV (10/4 cmH_20) in some lambs (24). 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 (30). 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 (16, 21). 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. The expected neural coordination between upper airway dilator muscles and diaphragm activity, where upper airway dilator activity precedes diaphragm activity (17), signifies that in nNAVA, the assist will always be delivered when the upper airways are open and "ready" to receive air insufflation from the ventilator. This may partly explain the better ventilator-patient interaction which has been recently reported in infants and children with nNAVA compared to nPSV (1, 38).

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 in order to further decrease the patient's inspiratory work (25). 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 muscle, which originates from below the larynx (33). 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 V_T value (figure 4), phasic inspiratory EAta was present in half of the lambs at PSV 15/4 but in none of the lambs at NAVA max. Coupled with our previous results (33), 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.

Enhancement of glottal constrictor muscle EMG activity by hypocapnia has been reported by several studies, especially during the post-inspiratory phase of the breathing cycle and during central apneas (18, 29, 39). Results from our previous studies however led us to hypothesize that the development of inspiratory EAta with increasing nIPPV was not related to a decrease in PCO_2 (24). Results from the present study, where special care was taken to assess PCO_2 variations more accurately, now suggest that the decrease in PCO_2, at times down to true hypocapnia (< 35 mmHg), may bear some responsibility in the development of inspiratory EAta during nPSV. However, our results also show that a decrease in PCO_2 is neither necessary nor sufficient for the development of inspiratory EAta during nIPPV. Overall, the present findings are in

agreement with previous suggestions that CO_2 level is only partly responsible for glottal narrowing under nIPPV and that mechanical factors (pressure, flow) probably also influence glottal behavior (26). Future studies will be needed to further delineate the importance of PCO_2 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 non-sedated newborn lambs, even at maximal achievable levels, appears as a further advantage compared to the widely used nPSV. While 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 in order to explore the physiological reasons behind this clear difference brought about by nNAVA.

ACKNOWLEGMENTS

The authors wish to fully acknowledge the excellent technical assistance of Norman Comtois and Jean-Philippe Gagné. This study was supported by the Canadian Institutes of Health Research (grant MOP 15558 allocated to JPP) and the Foundation of Stars. Jean-Paul Praud is the holder of the Canada Research Chair in Neonatal Respiratory Physiology and a member of the Centre de recherche clinique Étienne-Le Bel du Centre hospitalier universitaire de Sherbrooke. The Blom-Singer voice prostheses were graciously provided by InHealth Technologies, Carpinteria, CA, USA.

Author contributions

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FIGURE LEGENDS

Figure 1: Schematic representation of the experimental set-up in non-sedated, newborn lambs. Ptrach: tracheal pressure; $PetCO_2$: end tidal CO_2 pressure; EcoG: electrocorticogram; EOG: electrooculogram; TA: thyroarytenoid muscle; CT: cricothyroid muscle; EMG: electrical muscle activity.

Figure 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 one lamb. Contrary to NAVA max, PSV 20/4 triggers inspiratory EAta. Abbreviations: EAta: thyroarytenoid muscle EA; ∫EAta: moving time averaged EAta; EAct: cricothyroid muscle EMG; ∫EAct: moving time averaged EAct; EAdi: diaphragm EA; Pmask: mask pressure; Ptrach: tracheal pressure; Vlung: lung volume variations, given by the sum signal of respiratory inductance plethysmography (inspiration upwards); i: inspiration; e: expiration.

Figure 3: Variations of mask Pressure (Pmask) during: A) PSV (10/4, 15/4 and 20/4 cmH_2O) and B) NAVA (NAVA 1, NAVA 2 and NAVA max) mode in one 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 in order to study the highest possible peak inspiratory pressures in NAVA.

Figure 4: Variations of diaphragm energy expenditure and expiratory tidal volume (V_T, ml/kg) during nasal pressure support ventilation (nPSV) and neurally adjusted ventilatory assist (nNAVA).

Increasing the level of nPSV or nNAVA leads to a progressive decrease in the EAdi-time product (an indicator of diaphragm energy expenditure) (A) and a progressive increase in V_T. Note the higher V_T obtained with nPSV 20/4 vs. nNAVA max. Significant differences are indicated as *: vs. CPAP 4; †: vs. PSV 10/4; §: vs. PSV 15/4; ‡: vs. NAVA 1; #: vs. NAVA 2; ψ: vs. NAVA max.

Figure 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.

Figure 6: Phasic inspiratory thyroarytenoid muscle activity limits pressure transmission to the lungs at PSV 20/4 (left panel), contrary to observations at NAVA max (right panel) in the same lamb. See figure 1 for abbreviations. Pressures are given in cmH_2O.

TABLES

Table 1: Respiratory variables during nasal pressure support ventilation and Neurally Adjusted Ventilatory Assist

	Baseline		Pressure Support: PIP/PEEP (cmH_2O)			NAVA: Gain level		
	No CPAP	CPAP 4	10/4	15/4	20/4	NAVA 1	NAVA 2	NAVA max
RR_{vent} (breaths/min)	41 (10.5)	36.5 (8.5) $^{b\,c\,e\,f}$	34 (8) $^{b\,c}$	28 (7.5) ^{c}	20.5 (4)	32 (7.12) $^{e\,f}$	26.5 (5.24)	22.5 (5.5)
Pmask ($cm\ H_2O$)	0.1 (0.0)	7.1 (1.3)	11.5 (0.8)	16 (0.8)	21 (0.5)	11 (0.5)	14.5 (1.5)	17.5 (1.5)
Ptrach ($cm\ H_2O$)	1 (1)	6 (0.5)	10 (0.5)	14.5 (1)	18.5 (2)	10 (1)	14 (2)	16 (1.5)
PaO_2 (mmHg)	84 (12.5)	94 (10.5) ^{c}	93.5 (8) ^{c}	96.5 (9.5) ^{c}	106 (17)	100 (14)	101.5 (20)	96 (8.5)
$PaCO_2$ (mmHg)	46 (5)	44.5 (5) ^{c}	44 (7.5) ^{c}	43 (8) ^{c}	34.5 (6.5) ^{f}	44.5 (5.5)	45 (7.5)	43.5 (9)
$PetCO_2$ (mmHg)	51.5 (4.5)	52 (3.5) $^{b\,c\,f}$	50.5 (3.5) $^{b\,c}$	46.5 (4) ^{c}	40.5 (7.5) ^{f}	51 (4.5)	50 (4.5)	48 (6)
pH	7.37 (0.07)	7.38 (0.07) ^{c}	7.38 (0.04) $^{b\,c}$	7.4 (0.08) ^{c}	7.47 (0.15) ^{f}	7.37 (0.06)	7.37 (0.07) ^{f}	7.39 (0.08)
HCO_3^- (mmol/l)	26 (4.5)	26 (5)	26 (7.5)	26 (6.5)	24.5 (5)	25.5 (5)	26 (6)	26 (7)
EAdi-time product ($au.s.min^{-1}$)	299.8 (76)	225.9 (132) $^{b\,c\,d}$	185.1 (130) ^{b}	107.8 (67)	125.4 (62) ^{f}	279.1 (119) $^{e\,f}$	225.3 (91) ^{f}	195.3 (67)

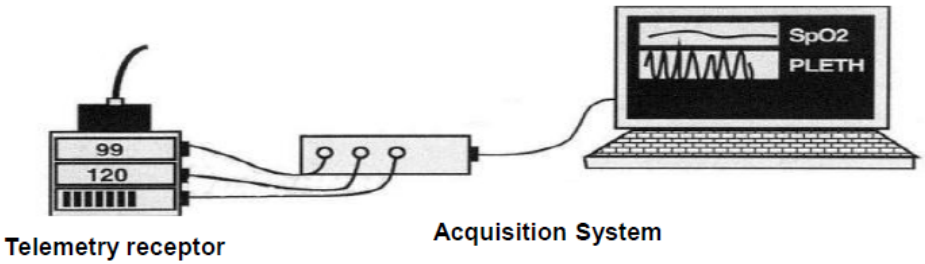
Values are reported as mean (standard deviation). RR: ventilator respiratory rate. Pmask: mask pressure; Ptrach: tracheal pressure; PIP: peak inspiratory pressure; PEEP: positive end-expiratory pressure; PaO_2: arterial O_2 pressure; $PaCO_2$: arterial CO_2 pressure; $PetCO_2$: end tidal CO_2 pressure; HCO_3^-: serum bicarbonates. EAdi-time product: diaphragmatic energy expenditure index. n = 8 lambs, except for PaO_2, $PaCO_2$, HCO_3^-, pH (7 lambs). Underlined exponent: $p < 0.05$; normal font exponent: $p < 0.1$. a: vs. PSV 10/4; b: vs. PSV 15/4; c: vs. PSV 20/4; d: vs. NAVA 1; e: vs. NAVA 2; f: vs. NAVA max.

Tableau 2: Percentage of respiratory cycles with inspiratory phasic activity of the thyroarytenoid muscle and $PaCO_2$ during nasal pressure support ventilation or neurally adjusted ventilatory assist (NAVA) in lambs during quiet sleep

	Nasal Pressure Support Ventilation						Nasal NAVA					
	10/4		15/4		20/4		NAVA 1		NAVA 2		NAVA max	
	%inspirEAta	$PaCO_2$	%inspirEAta	$PaCO_2$	%inspirEAta	$PaCO_2$	%inspirEAta	$PaCO_2$	%inspirEAta	$PaCO_2$	%inspirEAta	$PaCO_2$
lamb 1	0	-	44	-	100	-	0	-	0	-	0	-
lamb 2	51	40.5	57	40.5	100	36	0	41.5	0	46	0	41.5
lamb 3	0	53.5	0	50	0	30.5	0	51.5	0	52.5	0	45
lamb 4	0	38	0	43.5	0	38	0	42	0	45,5	0	40
lamb 5	17	55	30	50.5	22	26.5	0	50.5	0	53.5	0	60
lamb 6	0	35	33	30	62	29	0	38	0	35	0	31
lamb 7	0	40.5	0	36.5	100	39.5	0	39.5	0	35.5	0	39.5
lamb 8	0	45.5	0	49	0	44.5	0	49	0	46.5	0	46

%inspirEAta: percentage of ventilatory cycles with EAta.

Figure 1


SpO2
PLETH
99
120
Telemetry receptor
Acquisition System

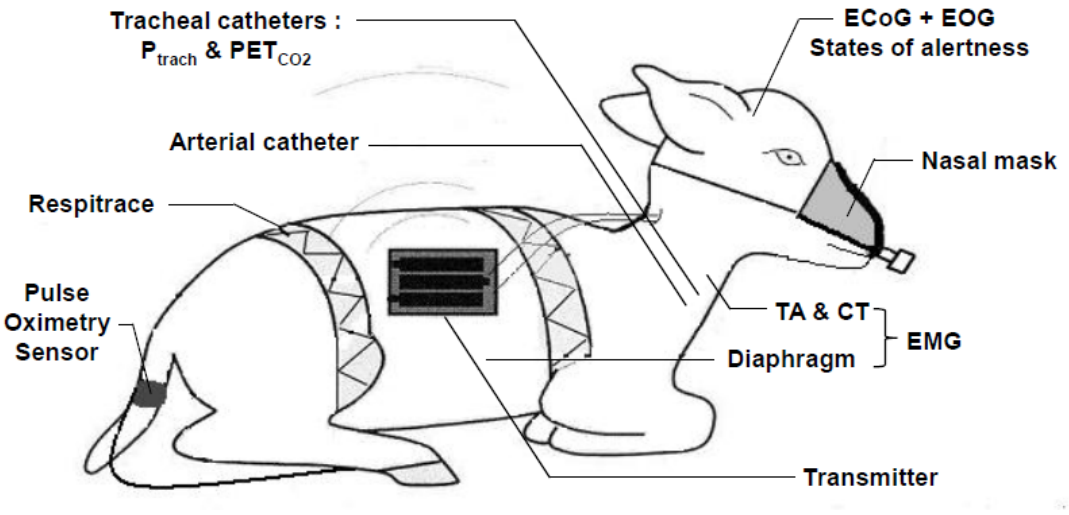

Tracheal catheters :
P_{trach} & PET_{CO2}
ECoG + EOG
States of alertness
Arterial catheter
Nasal mask
Respitrace
Pulse
Oximetry
Sensor
TA & CT
Diaphragm
EMG
Transmitter

Figure 2

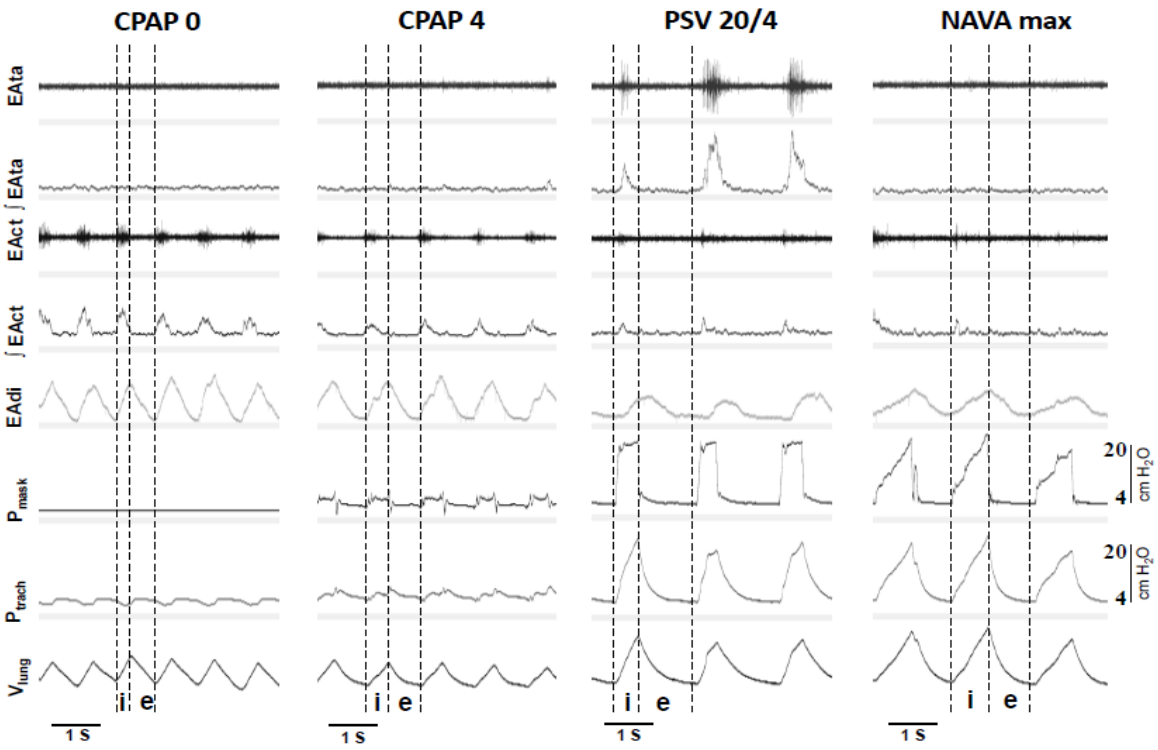

CPAP 0
CPAP 4
PSV 20/4
NAVA max
EAta
∫ EAta
EAct
∫ EAct
EAdi
P mask
P trach
V lung
20
4
cm H2O
i
e
1 s

Figure 3

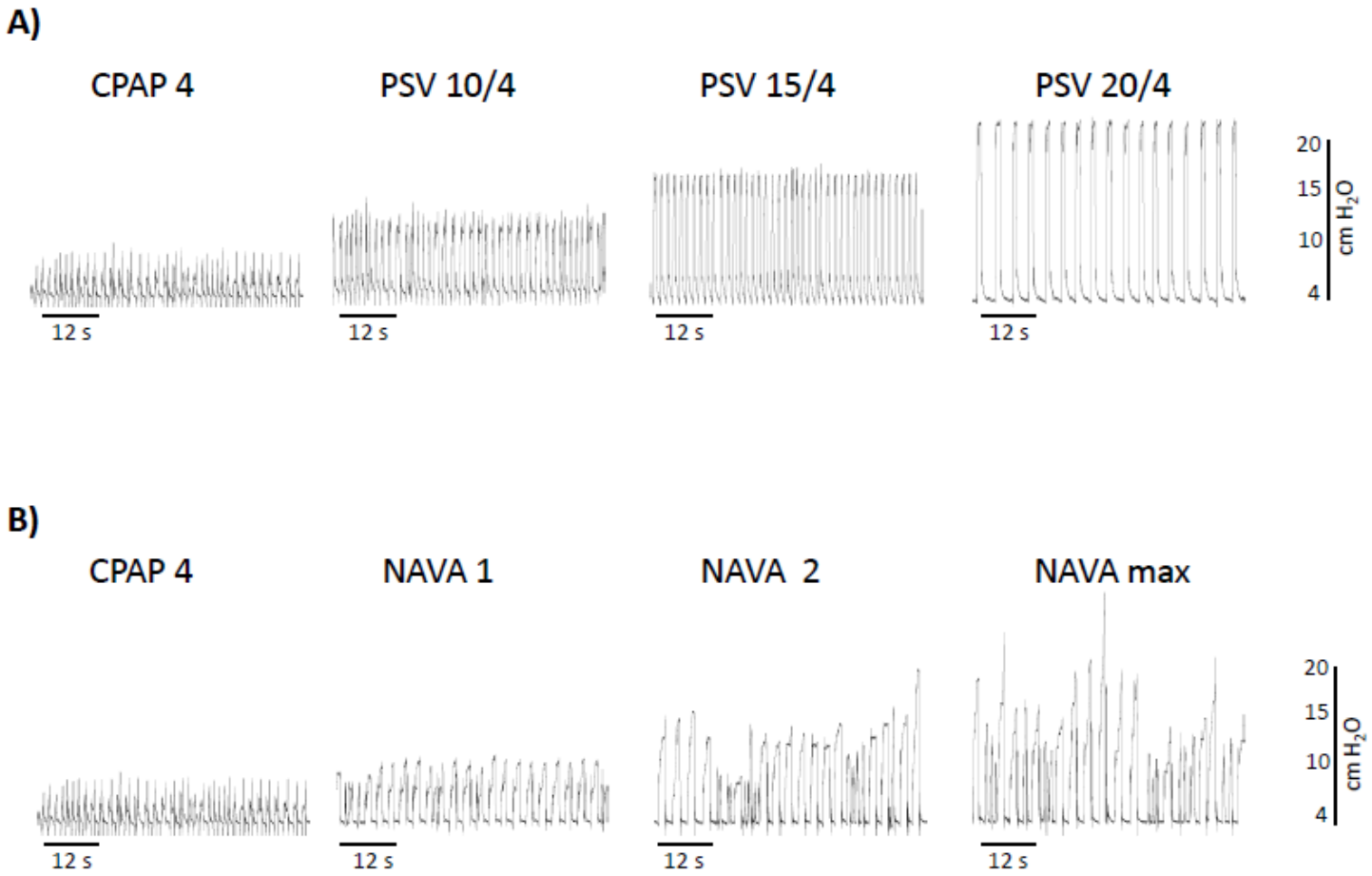

A)
CPAP 4
PSV 10/4
PSV 15/4
PSV 20/4
20
15
10
4
cm H2O
12 s
12 s
12 s
12 s
B)
CPAP 4
NAVA 1
NAVA 2
NAVA max
20
15
10
4
cm H2O
12 s
12 s
12 s
12 s

Figure 4

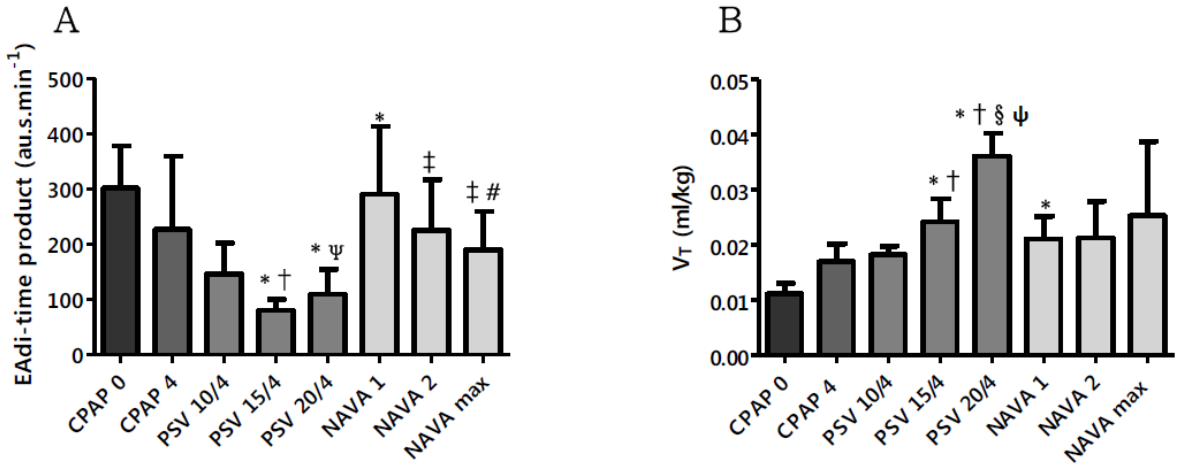

A
EAdi-time product (au.s.min-1)
500
400
300
200
100
0
* †
* Ψ
*
‡
‡ #
CPAP 0
CPAP 4
PSV 10/4
PSV 15/4
PSV 20/4
NAVA 1
NAVA 2
NAVA max
B
VT (ml/kg)
0.05
0.04
0.03
0.02
0.01
0.00
* †
* † § ψ
*
CPAP 0
CPAP 4
PSV 10/4
PSV 15/4
PSV 20/4
NAVA 1
NAVA 2
NAVA max

Figure 5

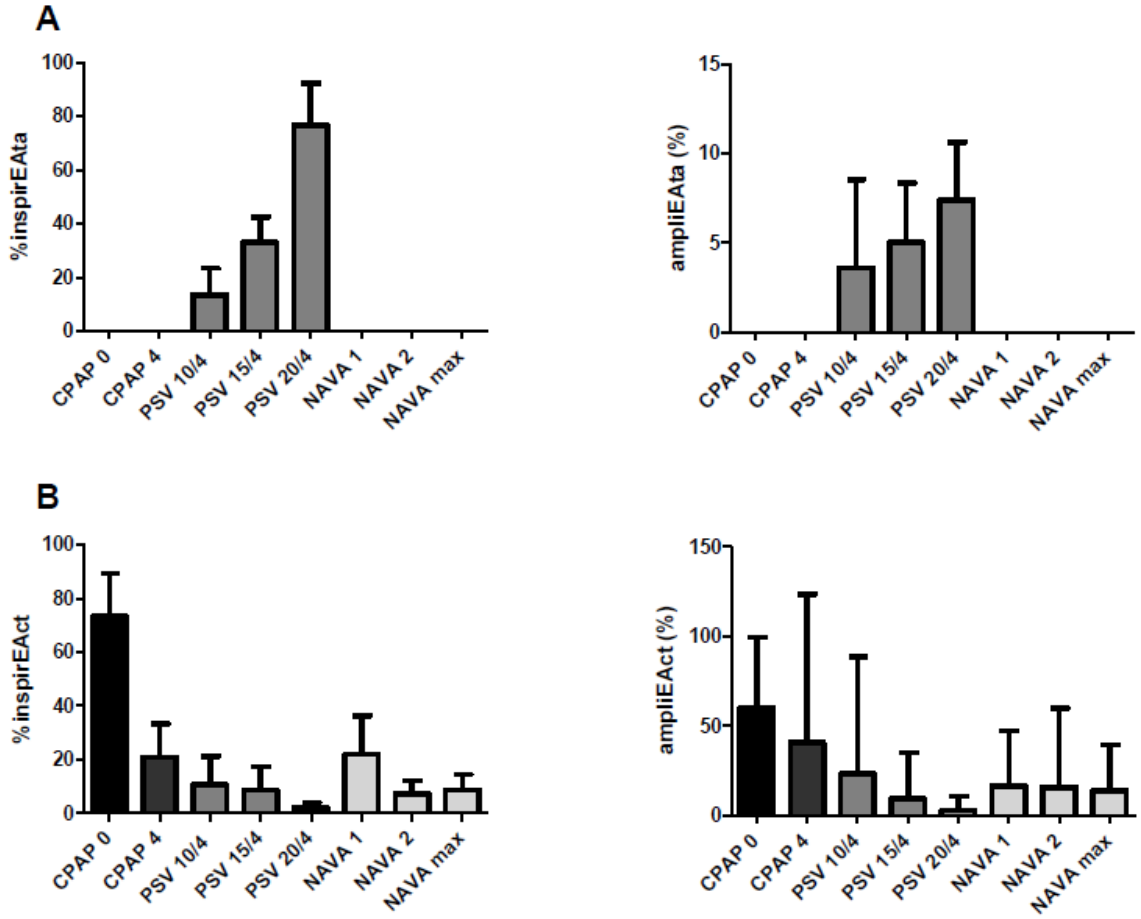
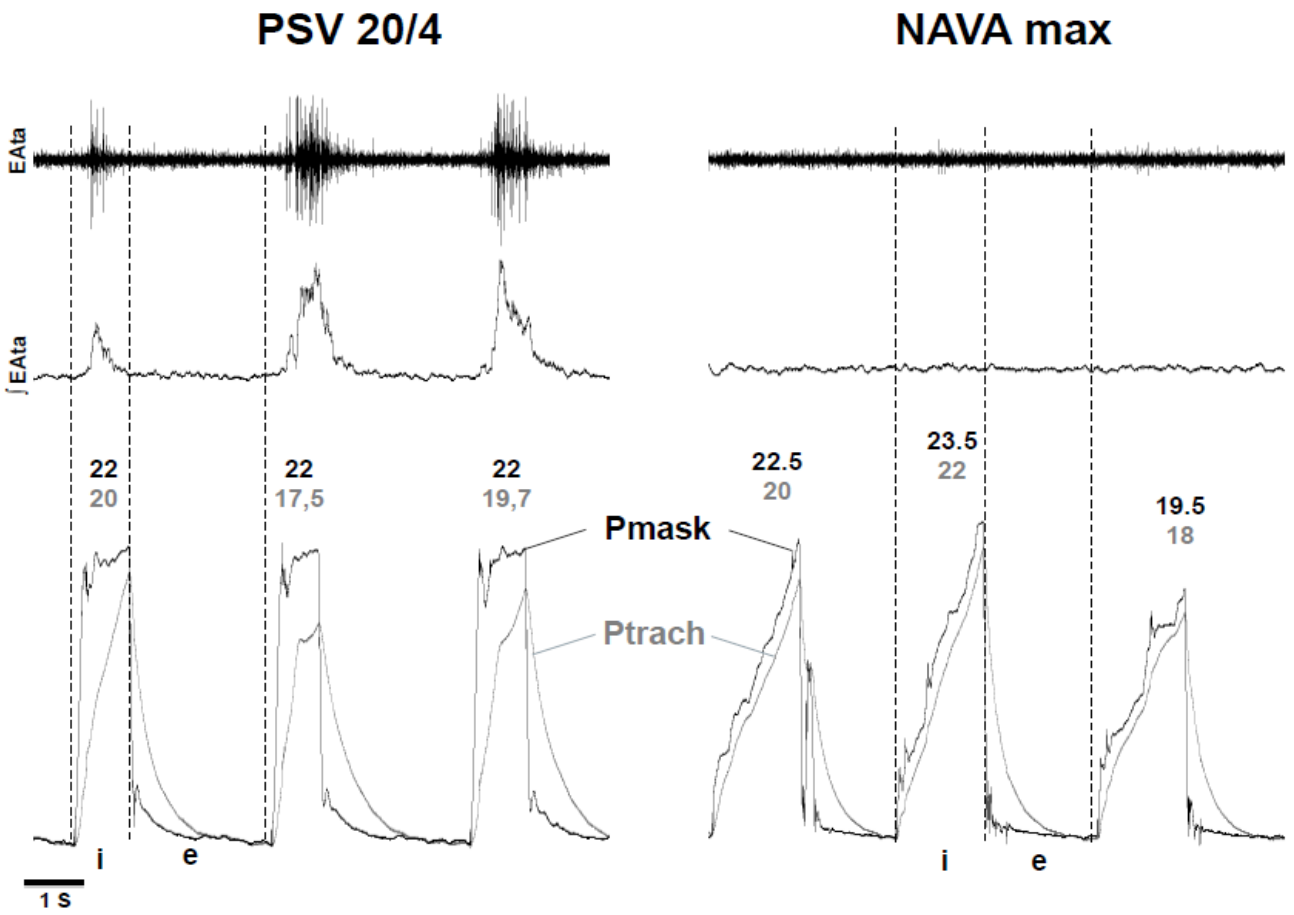

A
%inspirEAta
100
80
60
40
20
0
CPAP 0
CPAP 4
PSV 10/4
PSV 15/4
PSV 20/4
NAVA 1
NAVA 2
NAVA max
ampliEAta (%)
15
10
5
0
B
% inspirEAct
ampliEAct (%)
150
100
50

Figure 6


PSV 20/4
NAVA max
EAta
∫EAta
22
20
22
17,5
22
19,7
22.5
20
23.5
22
19.5
18
Pmask
Ptrach
i
e
i
e
1 s