Laryngeal muscle activity during nasal high frequency oscillatory ventilation in non-sedated newborn lambs

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Running head: High frequency ventilation and laryngeal muscle EMG

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ABSTRACT

Background - We have previously shown that nasal pressure support ventilation (nPSV) can lead to an active inspiratory laryngeal narrowing in lambs. This, in turn, can limit lung ventilation and divert air into the digestive system, with potentially deleterious consequences. On the other hand, nasal high frequency oscillatory ventilation (nHFOV) is particularly attractive in newborns, especially since, unlike nPSV, it does not require synchronization with the patient's inspiratory efforts.

Objectives - The main aim of the present study was to test the hypothesis that glottal constrictor muscle activity (EMG) does not develop during nHFOV. A secondary objective was to study laryngeal EMG during nHFOV-induced central apneas.

Methods - Polysomnographic recordings were performed in seven non-sedated lambs which were ventilated with increasing levels of nPSV and nHFOV at both 4 and 8 Hz, in random order. States of alertness, diaphragm and glottal muscle EMG, SpO2 and respiratory movements were continuously recorded.

Results - While phasic inspiratory glottal constrictor EMG appeared with increasing nPSV levels in 6 out of 7 lambs, it was never observed with nHFOV. In addition, nHFOV at 4Hz dramatically inhibited central respiratory drive in 4/7 lambs, with 64 to 100% of recording time spent in central apnea in 3 lambs. No glottal constrictor EMG was observed during these central apneas.

Conclusion - nHFOV does not induce glottal constrictor muscle EMG in non-sedated newborn lambs, in contrast to nPSV. This may be an additional advantage of nHFOV relative to nPSV.

KEYWORDS: Nasal pressure support ventilation, nasal high frequency oscillatory ventilation, polysomnography, central apnea, quiet sleep.

INTRODUCTION

Non-invasive ventilation is increasingly used in the newborns to reduce the duration of endotracheal mechanical ventilation and its associated complications. Common indications in infants for non-invasive ventilation include respiratory distress syndrome, apneas of prematurity and respiratory syncytial virus infection [1,2].

In addition to the various conventional non-invasive ventilation modalities available, nHFOV is attracting increasing interest. First, it is well established that *endotracheal* HFOV is associated with less lung injury than conventional mechanical ventilation in animal studies [3], as well as with superior lung function at 11 to 14 years of age in extremely prematurely-born children [4]. Secondly, nHFOV does not require synchronization with the patient's respiratory efforts, a strong advantage in the newborn [5]. Thirdly, case reports in newborns, as well as bench studies using lung models, have shown that nasopharyngeal HFOV is highly effective in eliminating CO2 [6,7]. Finally, animal data suggest that nasopharyngeal HFOV decreases lung inflammation and improves alveolarization compared to conventional ventilation [8].

However, an important consideration when using a nasal interface is the interposition of the larynx between the ventilator and the lungs. For instance, we have previously shown that nPSV can induce an active inspiratory laryngeal narrowing [9-11]. The latter may promote patient-ventilator asynchrony and limit lung ventilation [12], as well as divert the insufflated gas into the esophagus, exposing the infant to gastric distension and further respiratory compromise [13]. Knowing whether nHFOV can induce active laryngeal narrowing is certainly of interest before contemplating a more widespread use in newborns. Hence, the primary aim of our study was to assess the effects of nHFOV on

laryngeal EMG in non-sedated newborn lambs, testing the hypothesis that glottal narrowing does not develop during nHFOV.

Animal studies have demonstrated that *endotracheal* HFOV can inhibit spontaneous breathing and induce central apneas [14]. In addition, we have repeatedly shown the consistent presence of active glottal closure throughout central apneas in lambs [15]. Consequently, the secondary aims of the present study were to verify whether i) oscillation frequency changes during nHFOV induces central apneas and ii) active laryngeal closure is present during these nHFOV-induced central apneas.

MATERIAL AND METHODS

Animals

Experiments were conducted in seven term lambs aged from 4 to 5 days and weighing 80 4.1 kg (SD 0.7). The study was approved by the ethics committee for animal care and experimentation of the Universite de Sherbrooke (# 037-10).

Chronic instrumentation

Surgery was performed under general anesthesia for chronic instrumentation (see 11 for details). We measured the electrical activity of the thyroarytenoid (EAta, a glottal constrictor), cricothyroid (EAct, a laryngeal dilator) and sternal diaphragmatic (EAdi) muscles, states of alertness, arterial blood gases, respiratory movements (inductance plethysmography), oxygen hemoglobin saturation (SpO2) and mask pressure (Pmask). The raw EMG signals were sampled at 1000 Hz, band-pass filtered (30-300 Hz), rectified and moving time averaged (100 ms). All signals were transmitted *via* radiotelemetry and recorded using AcqKnowledge software (Santa Barbara, CA).

Design of study

Following 48 hours of rest, polysomnographic recordings were performed without sedation, while lambs were lying on their left side. Nasal PSV triggered by flow (Siemens Servo 300) and nHFOV (Sensormedics 3100a, Cardinal Health, Canada) were delivered *via* a custom-made nasal mask.

Following a first recording without ventilatory support (nCPAP 0), a nasal CPAP of 4 cmH2O was applied. Then, nPSV and nHFOV were applied in a random order, using a

step-by-step increase in ventilation. Three levels of nPSV (6, 11 and 16 cmH_2O above a PEEP of 4 cmH2O) were studied [9-11]. For nHFOV, preliminary experiments determined that while regular respiration was present at 8 Hz, respiration was frequently inhibited at 4 Hz. Hence, oscillatory frequency was first set at 8 Hz, mean airway pressure (MAP) at 8 cmH_2O and inspiratory time at 33% [7,16]; thereafter, power levels were progressively increased to match nPSV levels. Accordingly, nHFOV-8Hz-corresponded to the power level (ΔP-8Hz-1) at which abdominal vibrations were apparent, whereas nHFOV-$_{8Hz}$-2 and nHFOV-8Hz-3 corresponded to ΔP_{-8Hz}-1 + 10 and + 20 cmH_2O. Finally, nHFOV study was completed by reducing the oscillatory frequency to 4 Hz at nHFOV-$_{4Hz}$-3. At least five minutes of quiet sleep (QS) were recorded in each condition.

Data analysis

States of alertness: Standard electrophysiological and behavioral criteria were used to recognize states of alertness. Only periods of QS were analyzed for laryngeal EMG with nPSV and nHFOV. However, for the second aims of our study, all states of alertness were analyzed.

Respiratory dependent variables

At each ventilatory level, the first 60 seconds of continuous QS were analyzed. The percentages of breaths with inspiratory phasic EMG of the TA (%inspiEAta) or CT (%inspiEAct) were calculated [11]. The inspiratory phasic EAdi and EAct amplitudes were expressed as a percentage of EAdi or EAct values averaged over 60 seconds during nCPAP 0 (respectively %ampliEAdi and %ampliEAct). Finally, the minute-EAdi

(inspiratory phasic EAdi x respiratory rate) was calculated. Values were averaged over 60 seconds. Blood gases were measured at the end of each ventilatory level. A central apnea was defined as at least two missed breaths.

Statistical analysis

Results were averaged in each lamb, then averaged for the 7 lambs as a whole, and described as means and SD. The Friedman test followed by the Wilcoxon signed rank test was used for all analyses (SPSS statistics 20). Differences were considered significant if $P < 0.05$. In addition, a $P < 0.1$, indicative of a tendency towards a significant difference, was fully considered in the discussion.

RESULTS

Experiments were completed in all lambs. Sample tracings obtained in one lamb are shown in figure 1.

Alterations in respiration with increasing levels of nPSV and nHFOV at 8Hz

A significant decrease in respiratory rate (RR) was observed with increasing levels of nPSV and nHFOV$_{-8Hz}$ (Table 1). Overall, RR was decreased with nPSV 20/4 compared to nPSV 15/4 (P = 0.03), nPSV 10/4 (P = 0.02) and nCPAP 4 (P = 0.08). While no significant differences were observed between the various nHFOV$_{-8Hz}$ conditions (P = 0.2), RR was decreased in six lambs with nHFOV$_{-8Hz}$-3 compared to MAP 8. A significant decrease in %ampliEAdi (P = 0.05) and minute-EAdi (P = 0.04) (n = 4) was observed with increasing nPSV level, unlike nHFOV (Figure 2).

While $PaCO_2$ did not decrease during nHFOV (P = 0.9), $PaCO_2$ was significantly decreased at the highest nPSV level (20/4) compared to nCPAP 4, nPSV 10/4 and nPSV 15/4 (P between 0.02 and 0.04). No alteration of PaO_2 was observed (Table 1).

Laryngeal muscle activity with nPSV and nHFOV at 8Hz

Similarly to our previous studies, phasic inspiratory EAta (glottal constrictor) appeared with increasing levels of nPSV in 6 of 7 lambs (Table 2). In addition, %inspiEAta increased in proportion with nPSV levels (P = 0.01) (Figure 2). Simultaneously, a decrease in %inspiEAct and %ampliEAct (glottal dilator) was apparent with increasing levels of nPSV, although it did not reach statistical significance (respectively P ≥ 0.6) (Figure 2). Conversely to nPSV, inspiEAta was never observed at any nHFOV-8Hz level

in any of the lambs (Table 2, Figure 2). Simultaneously, no significant alteration of baseline %inspiEAct and %ampliEAct activity was apparent with nHFOV$_{-8Hz}$ (Figure 2).

Effects of nHFOV at 4Hz

Respiratory inhibition

The effects of a decrease in oscillatory frequency from 8 to 4 Hz are displayed in figure 1 and Table 3. Respiratory efforts were severely inhibited (> 60% recording time spent in apnea) in 3 of 7 lambs, including near total abolition of respiration throughout the recording in 2 lambs. Overall, the mean percentage of total time spent in apnea was higher at nHFOV$_{-4Hz}$-3 than nHFOV$_{-8Hz}$-3 (P = 0.02). In all lambs, regular respiration resumed when nHFOV$_{-4Hz}$-3 was ceased. Of note, despite the severe respiratory inhibition observed at nHFOV$_{-4Hz}$-3, PaCO2 remained above 35 mmHg for all lambs. In addition, $PaCO_2$ was not different at nHFOV$_{-8Hz}$-3 and nHFOV$_{-4Hz}$-3 (P = 0.4). Finally, the 2 lambs with the most marked decrease in $PaCO_2$ from MAP 8 to nHFOV$_{-4Hz}$-3 (lambs 2 and 5) had no respiratory inhibition at nHFOV$_{-4Hz}$-3. Hence, overall, higher respiratory inhibition at nHFOV$_{-4Hz}$-3 compared to nHFOV$_{-8Hz}$-3 was clearly not linked to a lower $PaCO_2$ in the former condition.

Laryngeal muscle activity

As documented during nHFOV-8Hz, no inspiratory or expiratory EAta was observed at nHFOV$_{-4Hz}$-3 during periods with respiratory efforts. Finally, no continuous EAta was observed during any central apnea induced by nHFOV$_{-4Hz}$-3.

DISCUSSION

This study demonstrates for the first time that in contrast to nPSV, nHFOV at 8 Hz or 4 Hz did not induce phasic inspiratory glottal constrictor activity in any lamb. Simultaneously, phasic inspiratory glottal dilator activity did not decrease during nHFOV, unlike nPSV. In addition, nHFOV at 4Hz dramatically inhibited spontaneous breathing in half of the lambs, while nHFOV at 8Hz was responsible for a lesser decrease in respiratory rate.

Respiration with nHFOV at 8 Hz

The use of HFOV via a nasopharyngeal tube has been reported in newborns [5,17,18]. Clinical interest in non-invasive HFOV stems from the fact that it does not require synchronization with the patient's breathing efforts [5]. In addition, HFOV is effective in eliminating CO_2 [6,7,19], while inducing less lung injury [3] and ensuring better alveolar development [8].

In agreement with observations in newborn infants [20], our results confirm that, aside from periods of prolonged central apneas which were especially prominent at 4 Hz (see infra), newborn lambs maintained regular respiration during nHFOV, with no significant modifications of baseline diaphragm activity.

Overall, blood gases were largely unaltered. The absence of hypocapnia may seem surprising, due to the reported ability of nHFOV to decrease CO_2 in newborn infants [6,7,19]. However, administration of nHFOV in these studies was for much longer periods than in our study, and the decrease in $PaCO_2$ was not apparent in the first two hours [7]. Further explanation may come from the absence of hypercapnia before

starting nHFOV in our lambs (except in one lamb), and the possibility of CO_2 re-inspiration [21].

Laryngeal muscle activity during nPSV and nHFOV

The present study confirms our previous results in lambs that inspiEAta often develops against ventilator insufflations during nPSV, likely from the stimulation of bronchopulmonary receptors [9-11]. In contrast to nPSV, phasic inspiEAta was absent during nHFOV. While high amplitude changes in pressure, flow and volume are transmitted to lower airways and lungs during ventilator insufflations in nPSV, the situation is very different in nHFOV, where forced oscillations of very small volumes are superimposed on a constant positive pressure. Hence, differences in pattern stimulation of bronchopulmonary receptors may explain the differences in EAta activity in nPSV *vs*. nHFOV. In addition, while stimulation of upper airway mechanoreceptors did not appear to be involved in the activation of glottal constrictor muscles in nPSV [10], the reported oscillatory activation of these mechanoreceptors may play a role in preventing inspiEAta in nHFOV [22-24]. Finally, given that inspiEAta during nPSV appears related to a decrease in $PaCO_2$ in some lambs [11], the absence of hypocapnia in nHFOV may be involved in the absence of inspiEAta.

A few studies have suggested that HFOV may stimulate active upper airway opening [22,23]. In the present study however, no modification of inspiratory glottal dilator activity (EAct) was apparent with nHFOV. These results suggest that nHFOV prevents active laryngeal closure also by maintaining inspiratory EAct.

Respiratory inhibiting effect of nHFOV at 4Hz

We observed that decreasing the oscillatory frequency from 8 to 4 Hz without altering MAP or Vt dramatically inhibited central inspiratory drive in almost all animals, without inducing hypocapnia. Similar respiratory inhibition reported with endotracheal HFOV has been linked to an increase in vagal pulmonary stretch receptor activity [14] as well as thoracic wall afferent activity [25]. While alterations of oscillation frequency, stroke volume or $PaCO_2$ have been deemed responsible for respiratory inhibition, our results show that alteration of frequency only in nHFOV can be sufficient.

Laryngeal muscle activity during induced apneas

Surprisingly, no continuous EAta was observed during any central apnea induced by nHFOV at 4Hz. Our studies have consistently shown the presence of active glottal closure throughout neonatal central apneas under various conditions. The latter include spontaneous apneas in full-term and preterm lambs, hypocapnic induced apneas, as well as apneas during anoxic gasping [15]. To date, nHFOV is the only condition during which continuous active glottal closure was absent during central apneas in our neonatal ovine models. This cannot be related to the absence of hypocapnia since the latter was obviously absent in anoxic gasping [26]. Hence, it is rather related to afferent messages originating from airway and/or thoracic wall mechanoreceptors stimulated by the constant positive pressure (MAP at 8 cmH2O) and/or ventilator oscillations. Again, the effect of high frequency oscillations in opening the upper airways may explain the absence of EAta during nHFOV-induced central apneas [22-24].

CONCLUSION

This is the first study documenting the effect of nHFOV on laryngeal muscle function and central inspiratory drive. In non-sedated newborn lambs, and contrary to nPSV, phasic inspiratory glottal constrictor activity is absent and phasic inspiratory glottal dilator activity is maintained during nHFOV. Moreover, nHFOV at 4 Hz often dramatically inhibits central inspiratory drive, even in the absence of alveolar hyperventilation. Further studies are needed to clarify the exact reflex mechanism underlying this respiratory inhibition. We propose that our results are relevant in helping the clinician choose the optimal nasal ventilatory modality for a given newborn in need of ventilatory support.

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FIGURE LEGENDS

Figure 1: Laryngeal muscle activity during nasal support ventilation (nPSV) and nasal high frequency oscillatory ventilation (nHFOV) at 8 Hz during quiet sleep in one lamb. In contrast to nPSV 15/4, nHFOV$_{-8Hz}$-3 does not induce phasic inspiratory glottal constrictor electrical activity. Abbreviations from top to bottom: EAta, electrical activity (EA) of the thyroarytenoid muscle (ta, a glottal constrictor); ∫EAta, moving time averaged EAta; EADi, EA of the diaphragm muscle; Pmask, mask pressure; Vlung, lung volume variations, given by the sum signal of the respiratory inductance plethysmography (inspiration upwards); I, inspiration; e, expiration. Arterial CO_2 pressure ($PaCO_2$) is given in mmHg and heart rate (HR) in bpm. In addition to the inspiratory phasic EAta, which consistently occurred in lambs with nPSV in the present study as well as in our previous studies, expiratory phasic EAta was also uniquely observed in this lamb. Such expiratory EAta was very rarely observed in our previous studies on nPSV.

Figure 2: Glottal constrictor (EAta), glottal dilator (EAct) and diaphragmatic muscle electrical activity (EAdi) during nPSV and nHFOV-$_{8Hz}$. A) Percentage of ventilatory cycles with EAta (%inspiEAta) for 6 lambs. B) Inspiratory phasic EAct amplitude (%ampliEAct) calculated for each inspiration and expressed as a percentage of EAct values during nCPAP 0 for 5 lambs C) Inspiratory phasic EAdi amplitude calculated for each inspiration and expressed as a percentage of EAdi values during nCPAP 0 (%ampliEAdi), as well as minute-EAdi for 4 lambs. Increasing nPSV levels, as opposed to nHFOV, led to a progressive increase in %inspiEAta. While not statistically significant,

362 a decrease in %ampliEAct was apparent with increasing levels of nPSV, whereas this
363 activity remained unchanged during nHFOV. Finally, a significant decrease in both
364 %ampliEAdi and minute-EAdi was observed with increasing nPSV level, unlike nHFOV
365 mode. Underlined exponent: $P < 0.05$; normal font exponent: $P < 0.1$ ∞: vs. CPAP 0; †:
366 vs. PSV 10/4.; ℓ: vs. PSV 15/4.
367

TABLES

Table 1: Respiratory variables during nasal pressure support ventilation and high frequency oscillatory ventilation

	Baseline		nPSV: PIP/PEEP (cmH_2O)			nHFOV			
	nCPAP 0	nCPAP 4	10/4	15/4	20/4	MAP 8	8Hz-1	8Hz-2	8Hz-3
PaO_2 (mmHg)	73 (9)	79 (12)	85 (15)	87 (19)	83 (24)	83 (13)	94 (30)	88 (12)	84 (15)
$PaCO_2$ (mmHg)	44 (8)	44 (8)	44 (7)	43 (8)	39 (8) [a, b, c]	46 (7)	44 (10)	45 (10)	44 (8)
pHa	7.41 (0.04)	7.39 (0.04)	7.37 (0.05)	7.39 (0.06)	7.43 (0,09) [a, b]	7.38 (0.05)	7.38 (0.05)	7.39 (0.04)	7.38 (0.04)
RR (breaths/min)	57 (17)	49 (19)	58 (34) [c]	42 (30)	36 (26) [a, b, c]	53 (34)	67 (59)	53 (53)	30 (12)
Pmask ($cm\ H_2O$)	1 (1)	7 (1)	10 (1)	16 (1)	21 (1)	8 (1)	9 (4)	8 (2)	9 (2)

Values are reported as mean (standard deviation). nPSV: nasal pressure support ventilation; PIP: peak inspiratory pressure; PEEP: positive end-expiratory pressure; nHFOV: nasal high frequency oscillatory ventilation. nCPAP: nasal continuous positive airway pressure; MAP: mean airway pressure. 8Hz: oscillation frequency at 8 Hz, with 8Hz-1, 8Hz-2, 8Hz-3 indicating increasing power levels (ΔP-1, ΔP-2, ΔP-3); PaO_2: arterial O_2 pressure; $PaCO_2$: arterial CO_2 pressure; pHa: arterial pH; RR: respiratory rate; Pmask: mask pressure. Underlined exponent: $p < 0.05$; normal font exponent: $p < 0.1$. a: vs. CPAP 4; b: vs. PSV 10/4; c: vs. PSV 15/4.

Table 2: Percentage of respiratory cycles with inspiratory phasic activity of the thyroarytenoid muscle and $PaCO_2$ during nasal pressure support ventilation or high frequency oscillatory ventilation in lambs during quiet sleep

	Nasal Pressure: PIP/PEEP (cmH_2O)						nHFOV power levels (cmH_2O)							
	10/4		15/4		20/4		$nHFOV_{-8Hz}$-1		$nHFOV_{-8Hz}$-2		$nHFOV_{-8Hz}$-3		$nHFOV_{-4Hz}$-3	
	%inspiEAta	$PaCO_2$ mmHg	%inspiEAta	$PaCO_2$ mmHg	%inspiEAta	$PaCO_2$ mmHg	%inspiEAta	$PaCO_2$ mmHg	%inspiEAta	$PaCO_2$ mmHg	%inspiEAta	$PaCO_2$ mmHg	%inspiEAta	$PaCO_2$ mmHg
lamb 1	0	35.5	24	35.5	17	35.5	0	30	0	36.5	0	37.5	0	38.5
lamb 2	0	46	30	43.5	77	42.5	0	48	0	46	0	47	0	39
lamb 3	88	39	100	36.5	100	36.5	0	38.5	0	36.5	0	39.5	0	39.5
lamb 4	0	40.5	0	41.5	100	27.5	0	44	0	41.5	0	38.5	0	38.5
lamb 5	0	43.5	0	44.5	0	39	0	38	0	42	0	41	0	36.5
lamb 6	0	57.5	0	58.5	32	53.5	0	62.5	0	66	0	59.5	0	60.5
lamb 7	0	45	65	43	86	41.5	0	48	0	48	0	44	0	43

%inspiEAta: percentage of ventilatory cycles with EAta during inspiration. See table 1 for other abbreviations.

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371

Table 3: Effects of oscillatory frequency on respiratory efforts

	$nHFOV_{-8Hz}$-3						$nHFOV_{-4Hz}$-3					
	time in apnea (s)	% time in apnea	% QS in apnea	% W in apnea	RR (/min)	$\Delta PaCO_2$ (mmHg)	time in apnea (s)	% time in apnea	% QS in apnea	% W in apnea	RR (/min)	$\Delta PaCO_2$ (mmHg)
Lamb 1	8/993	1	1	1	43	- 2	266/417	64	71	56	-	- 1
Lamb 2	0/541	0	0	0	28	- 1	11/917	1	1	3	26	- 9
Lamb 3	19/1041	2	0	4	29	- 1	340/340	100	100	100	-	- 1
Lamb 4	6/874	1	0	2	29	- 3	63/415	15	0	38	24	- 3
Lamb 5	4/463	1	2	0	39	- 2	10/411	2	0	8	33	- 7
Lamb 6	0/1222	0	0	0	40	- 2	97/353	27	16	62	-	- 1
Lamb 7	228/1158	20	19	28	7	- 3	373/432	86	85	95	-	- 4
Mean ± SD		3 ± 7	3 ± 7	5 ± 10	31 ± 12	- 2 ± 1		42 ± 41	39 ± 44	52 ± 38	28 ± 5	- 4 ± 3

Abbreviations: $nHFOV_{-8Hz}$-3 or $_{-4Hz}$-3: nasal high frequency oscillatory ventilation at 8 Hz and 4 Hz respectively, with power level ΔP-3; time in apnea (s): total time spent in apnea during total recording; % time in apnea: percentage of total recording time spent in apnea; % QS (or W) in apnea: percentage of quiet sleep (or wakefulness) time spent in apnea; RR: respiratory rate calculated for each lamb presenting a % time in apnea less than 20%; $\Delta PaCO_2$: difference of $PaCO_2$ between MAP 8 and $nHFOV_{-8Hz}$-3 (or $nHFOV_{-4Hz}$-3) conditions.

FIGURES

Figure 1

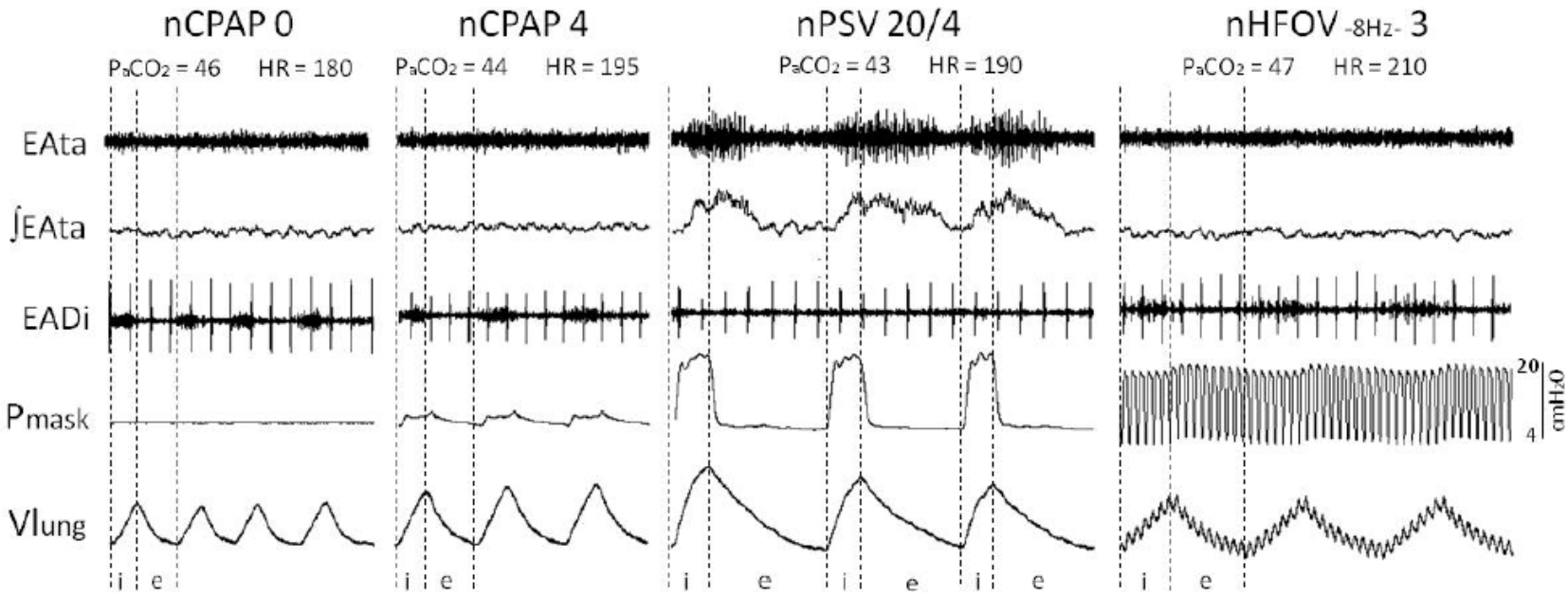
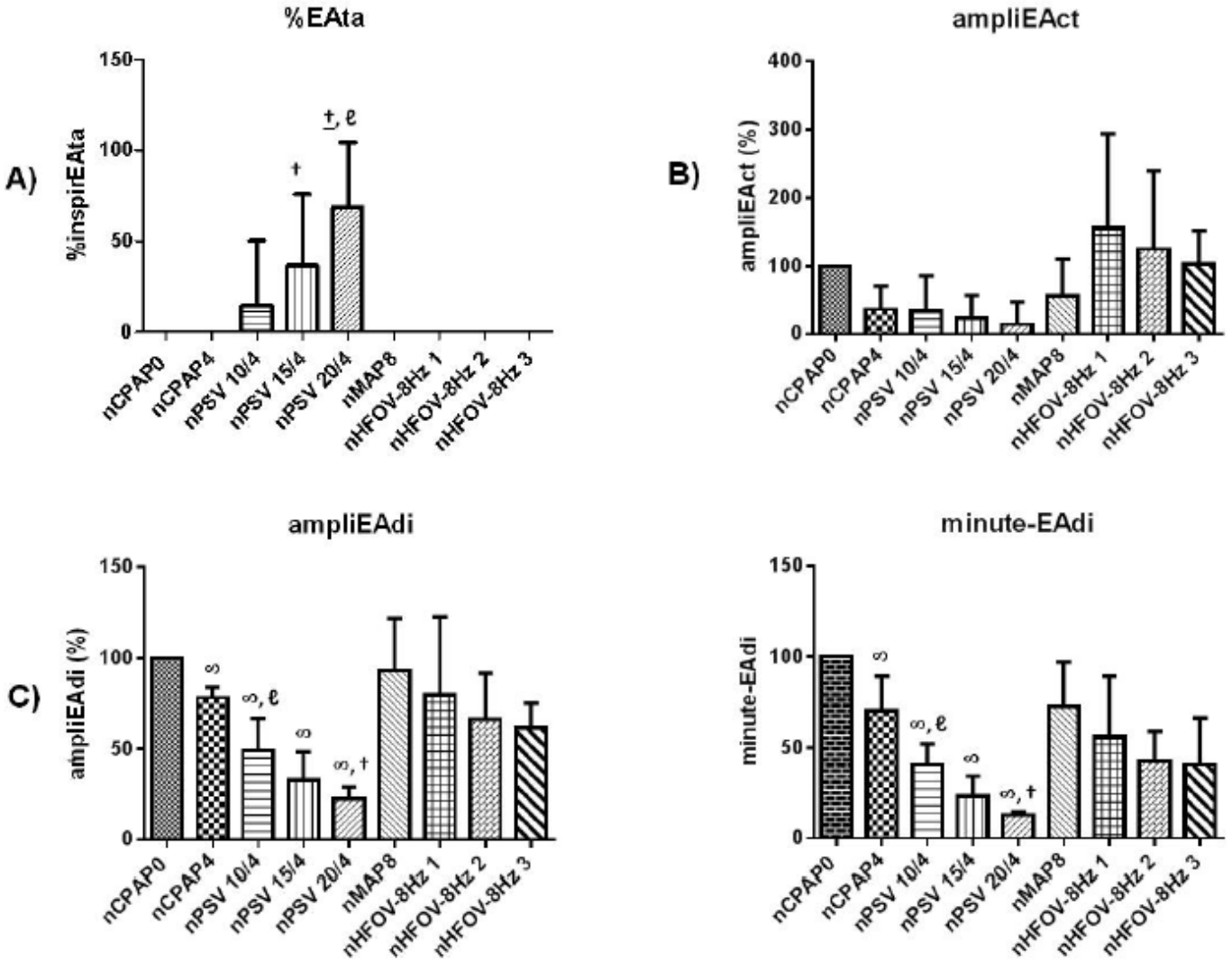


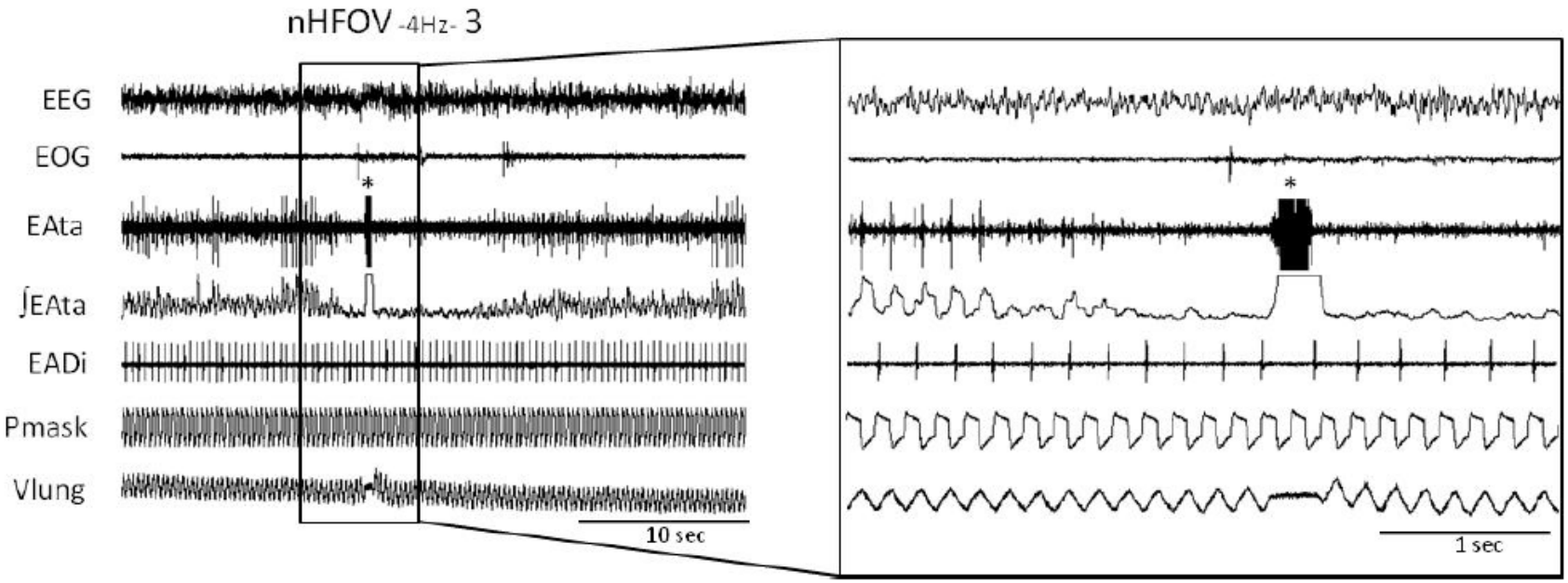
Figure 2:


A)
%EAta
%inspirEAta
150
100
50
0
†
†, ℓ
nCPAP0
nCPAP4
nPSV 10/4
nPSV 15/4
nPSV 20/4
nMAP8
nHFOV-8Hz 1
nHFOV-8Hz 2
nHFOV-8Hz 3
B)
ampliEAct
ampliEAct (%)
400
300
200
100
0
C)
ampliEAdi
ampliEAdi (%)
150
100
50
0
§
§, ℓ
§
§, †
minute-EAdi
minute-EAdi
150
100
50
0
§
§, ℓ
§
§, †

378

379

Figure 3:



380