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Influence of Proportional Assist Ventilation on Diaphragmatic Activity in Normal Subjects

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Abstract: In six awake healthy adults we studied the physiological effects of mechanical unloading of the respiratory muscles during increased ventilatory demand. We were interested in whether respiratory muscle activity is down regulated and if this is mainly a consequence of chemical factors, i.e. CO_2-reduction, or non-chemical neuromuscular inhibition. With 33 mmHg inspiratory CO_2 we induced modest hyperpnea of 24.4 ± 3.9 L/min. Proportional assist ventilation (PAV) was applied with flow-related assist of 2.5 cm H_2O/L/s and volume-related assist of 6 cm H_2O/L. Respiratory muscle activity was measured by transdiaphragmatic pressure. Unloading caused a 57 percent reduction of the inspiratory transdiaphragmatic pressure-time product ($p<0.05$), while tidal volume, breathing frequency, and breathing pattern did not significantly change. These observations suggest that during increased ventilatory requirements, PAV results in down regulation of respiratory muscle activity and that this effect is mainly a consequence of neuromechanical inhibition.

Key words: control of breathing; respiratory muscles; carbon dioxide; unloading; proportional assist ventilation

Introduction

Proportional assist ventilation (PAV) is a new form of inspiratory assistance that can be used for the treatment of acute and chronic respiratory failure in spontaneously breathing patients. Although active inspiration is needed to trigger the ventilator, several studies have shown that PAV can effectively reduce respiratory muscle activity [14, 19]. The physiological mechanism of this effect, however, is not well understood. Since inspiratory assistance can increase ventilation with a consecutive reduction of arterial PCO_2, the unloading effect might be a result mainly of chemical influences [24]. Alternatively, the respiratory muscles might be unloaded by a non-chemical mechanism, commonly referred to as neuromechanical inhibition [4].

Results of former investigations which were performed to elucidate the physiological mechanism of respiratory muscle unloading are inconclusive. Investigations in awake healthy subjects are difficult to interpret, because inspiratory assistance stimulates breathing and induces profound hypocapnia [10, 13]. Recently however, Faroux et al. [5] have shown that the respiratory muscles are also unloaded when end-tidal CO_2 is kept stable during pressure support ventilation (PSV). In contrast, Georgopoulos et al [9] have observed no reduction in respiratory muscle activity, when PAV was applied during CO_2-stimulated breathing.

The aim of our study was to evaluate the effects of PAV on respiratory muscle activity and ventilation during increased ventilatory requirements. Breathing was stimulated with increased inspiratory CO_2 (steady state), while respiratory muscle unloading was performed with PAV. We used PAV, because, in contrast to PSV, the ventilator pressure output is proportional to the subjects breathing effort [25]. Therefore, this mode of inspiratory assistance might provide a better control of breathing.

Methods

Subjects

Six healthy non-smoking male volunteers were studied (Table 1) after giving written consent to a protocol approved by the ethics committee of the Philipps-University Marburg. Subjects were students and members of the laboratory staff, who were familiar with the procedures, required for the investigation but were unaware of its specific purpose.

Description of the Ventilator

Mechanical ventilation was provided using a small ventilator, designated for non-invasive ventilation, which can be set to deliver several modes of assisted ventilatory support (prototype from Respironics Inc., Murrysville PA, USA). In the PAV-mode the gas delivery system provides flow-related assist and volume-related assist proportional to the subjects demand [25]. PAV was implemented with arbitrary values for elastance and resistance compensation to achieve partial unloading of the respiratory muscles: volume assist was set to 6 cm H_2O/L and flow assist to 2.5 cm H_2O/L/s, with the lowest constant baseline pressure during expiration provided by this device, which is around 2 cm H_2O.

Table 1. Subject characteristics.

Subject	Age	Height	Weight	FEV1	VC	FRC	Raw	PO_2	PCO_2
	yr	cm	kg	% pred	% pred	% pred	kPa*s/L	mmHg	mmHg
1	25	189	82	109	97	119	0.16	87	38
2	25	190	83	120	102	148	0.13	84	40
3	27	186	84	96	92	119	0.13	84	41
4	32	190	92	118	118	125	0.15	86	39
5	42	180	71	100	97	102	0.12	88	38
6	27	184	85	110	108	112	0.13	85	39
Mean	30	187	83	109	102	121	0.14	86	39
+ SD	7	4	7	10	9	15	0.02	2	1

Definition of abbreviations: FEV1 = forced expiratory volume in one second; VC = vital capacity; FRC = functional residual capacity; Raw = airway resistance; PO_2 = capillary oxygen tension; PCO_2 = capillary carbone dioxyde tension.

Measurements

Subjects were connected to the ventilator using a single-channel tubing with a built-in leak and a commercial nose mask (Respironics, Inc., Murrysville PA, USA). Pressure at the airway opening (Paw) was measured at a side-port of the nose mask with a piezoelectric pressure transducer (143PC03D, Microswitch). An infrared capnograph (Novametrix Capnograph 7000, Wallingford, Connecticut, USA) to measure inspiratory and expiratory PCO_2 and a variable orifice flow-sensor (Bicore, Irvine, CA, USA) to measure airflow were placed between the built-in leak of the ventilator circuit and the nose mask. The pressure drop across the two ports of the pneumotachograph was measured with a differential piezoelectric pressure transducer (163PC01D36, ± 12.7 cm H_2O; Microswitch, Freeport Illinois, USA). Because the variable orifice sensor produces a differential pressure signal non-linear to airflow, linearisation of this signal was performed by means of a microcomputer constructed to convert the pressure signal into flow (Biscope, Sing Medical, Stäfa, Switzerland). Combined resistance of the nose mask and the flow-sensor when applied to the subject was measured as R = K1 + K2V', adapted from the Rohrer's equation Pres = K1V' + K2V', where Pres = resistive pressure (kPa), V' = airflow (L/s), K1 = coefficient of linear resistance, K2 = coefficient of non-linear resistance: for inspiration K1 = 0.26, K2 = 0,10 and for expiration K1 =0.17, K2 = 0.12. Deadspace of the nose mask plus flow-sensor was 90 ml.

Respiratory effort was evaluated by measuring esophageal (Pes) and gastric (Pga) pressure. A catheter with two piezo crystal pressure transducers (GaelTec, Dunvegan, Isle of Skye, UK) was advanced until both transducers were located intragastrically and then withdrawn until opposite phase directions appeared during inspiratory efforts, indicating placement of the Pes transducer at the gastro-esophageal junction. A previous investigation showed that transpulmonary pressure measured with this system correlates well with measurements obtained with balloon catheters [16]. The catheter was then withdrawn approximately 10 cm until minimal cardiac artefacts were present and optimal correlations of Paw and Pes were recorded by means of the occlusion test [2]. The catheter was fixed to the nose by non-elastic tape to prevent dislocation.

The flow and pressure signals were sampled at a rate of 100 Hz and the PCO_2 signal at a rate of 25 Hz, using a computer data acquisition system with a built-in 16-bit analogue-to-digital converter. The collected data were stored on optical disc for subsequent analysis. All variables were also recorded on a 16-channel strip chart recorder (Picker, München, Germany) at a paper speed of 10 mm/sec. The flow signal was corrected for changes in gas temperature and gas composition. All pressure channels were calibrated using a water manometer.

Study protocol and Data Analysis

All investigations were performed in the morning at least two hours after a light breakfast without caffeine intake. Subjects were studied lying in a semi-supine position (45°). The nose mask was firmly attached. Performance of the occlusion test assured that no air leaks were present. Baseline conditions of CO_2-stimulated breathing were achieved by exposing the subjects to a hypercapnic and normoxic gas mixture. For this purpose the blenders were adjusted to provide an inspiratory PCO_2 level of 33 mm Hg, while FiO_2 (fraction of inspired oxygen) was held constant at 0.21 (Fig.1). Subjects were exposed to continuous flow with this gas mixture by setting the ventilator in the lowest level (approximately 2.0 cm H_2O) of the CPAP mode. After 15 minutes breathing CO_2-enriched air (control period 1), PAV support was applied for 15 min, followed by a second 15 min period of unsupported breathing (control period 2). During the runs readjustments at the gas delivery system provided constant levels of inspiratory PO_2 and PCO_2.

Measurements were obtained from at least 20 breaths during the last two minutes of each experimental condition. Tidal volume (VT) was obtained by integration of the flow signal. Volume calibration at several flow rates was performed with a one litre syringe. Duration of inspiration (TI) and expiration (TE) was analysed from the flow signal. Minute ventilation

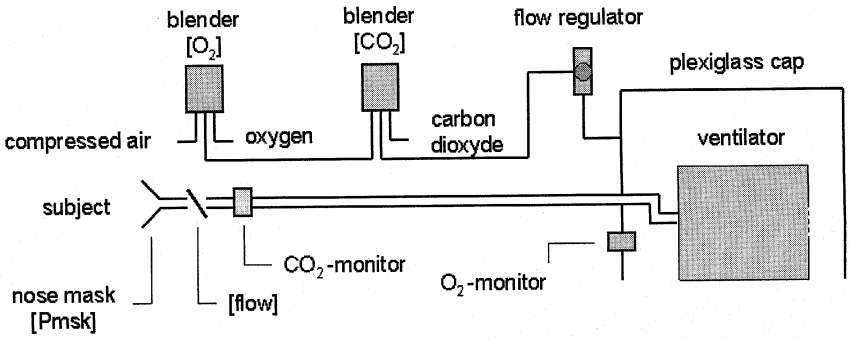

Fig. 1. Schematic diagram of the experimental setting. The ventilator is positioned under a plastic cap, where a constant milieu of carbon dioxide (CO_2)-enriched air is provided by means of blenders for oxygen (O_2) and CO_2. Gas composition is controlled by an oxymeter (O_2 monitor) and a capnograph (CO_2 monitor). See text for further details.

(V'E) was determined from the product of VT and breathing frequency (f). Dynamic positive end-expiratory pressure (PEEPi) was measured as esophageal pressure change between the beginning of the abrupt pressure decay in Pes, indicating the start of inspiration and the point where flow reaches the zero line. This method of estimating PEEPi in spontaneous breathing subjects is based on the assumption that the change in pleural pressure required to start inspiratory airflow approximates the end-expiratory elastic recoil pressure of the respiratory system, provided that the expiratory muscles are relaxed during expiration [15, 20]. Transdiaphragmatic pressure (Pdi) was calculated as Pga minus Pes, including PEEPi. The inspiratory diaphragmatic pressure-time product (PTPdi) was obtained by electronically integrating Pdi from the end-expiratory baseline over mechanical TI and calculated per minute or per minute volume [17].

All data are expressed as mean ± SD. Results from the PAV tests and the control tests of unsupported breathing were compared with analysis of variance for repeated measures (ANOVA). When the F value was significant, Wilcoxon rank sum test was used to identify significant differences. Significance was assumed at p values <0.05.

Results

All subjects completed the experiment successfully. CO_2-stimulation induced a moderate and variable increase in minute ventilation by 24.4 ± 3.9 (range 19.9-31.5) L/min.

End-tidal CO_2 ($PETCO_2$) decreased non-significantly by 1.2 mm Hg during PAV compared to unsupported breathing. The individual effect, however was variable. In 3/6 experiments $PETCO_2$ was slightly increased rather than decreased. Neither tidal volume, nor breathing frequency or breathing pattern changed with PAV (Table 2).

Compared to unsupported spontaneous breathing PAV induced a prompt reduction in Pes and Pdi within one to five breaths in all subjects. The effect of PAV on respiratory muscle effort for one representative subject is demonstrated in Figure 2: the amplitudes in Pes and Pdi increased immediately when inspiratory assistance was switched off. With PAV PTPdi decreased in each individual subject, regardless if values were calculated per minute or per minute ventilation (Table 3). These results indicate that muscle effort and work of breathing were effectively reduced.

We observed PEEPi around 0.3 kPa during spontaneous breathing. With PAV PEEPi was slightly, but not significantly reduced (Table 3). No active expiratory muscle activity was noticed from the Pga tracings.

Discussion

We subjected healthy volunteers to increased inspiratory CO_2 to stimulate breathing. With PAV inspiratory muscle effort was effectively reduced, while ventilation was not increased. It follows, that respiratory muscle unloading was not mainly a consequence of hyperven-

Table 2. Changes of breathing pattern and $PETCO_2$ with PAV.

	Control 1	PAV	Control 2	p value (ANOVA)
VT	1.62 + 0.39	1.57 + 3.39	1.55 + 0.44	NS
f	15.3 + 1.1	15.7 + 3.2	15.7 + 1.9	NS
V'E	24.40 + 3.94	24.27 + 6.09	23.61 + 3.82	NS
TI	1.74 + 0.18	1.71 + 0.35	1.72 + 0.22	NS
TE	2.22 + 0.19	2.26 + 0.47	2.18 + 0.28	NS
TI/Ttot	0.44 + 0.02	0.43 + 0.04	0.44 + 0.01	NS
VT/TI	0.94 + 0.15	0.93 + 0.21	0.89 + 0.15	NS
$PETCO_2$	44.3 + 2.0	43.0 + 2.1	44.0 + 2.4	NS

Definition of abbreviations: PAV = proportional assist ventilation; VT = expired tidal volume (L); f = breathing frequency (1/min); V'E = expired minute ventilation (L/min); TI = inspiratory time (s); TE = expiratory time (s); TI/Ttot =inspiratory duty cycle; VT/TI = mean inspiratory flow (L/s); $PETCO_2$ = partial pressure of end-tidal PCO_2 (mm Hg).
Values are mean + SD for 6 subjects.

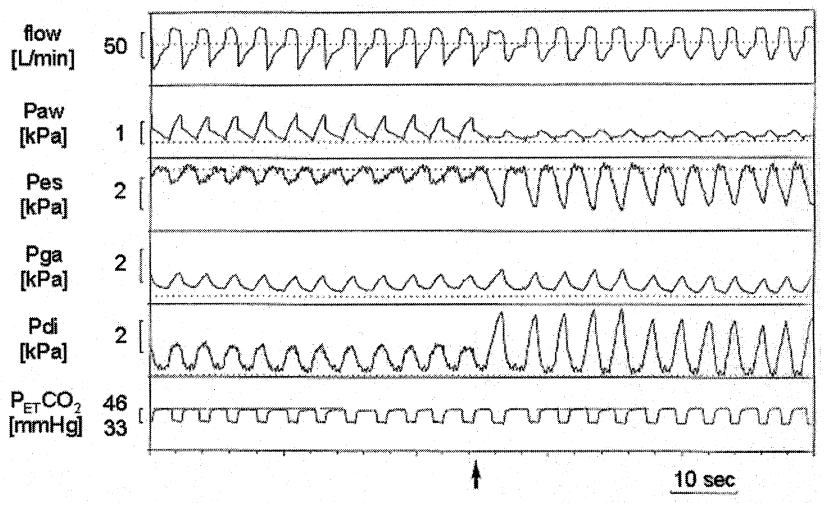

Fig. 2. Tracings obtained in one representative subject during CO_2-stimulation shows transition from supported breathing with PAV to unsupported spontaneous breathing. From top to bottom: Airflow (Flow), pressure at the airway opening (Paw), esophageal pressure (Pes), gastric pressure (Pga), transdiaphragmatic pressure (Pdi) and carbon dioxide tension ($PETCO_2$). Dotted lines in the airflow and pressure tracings indicate zero levels; dotted line in the $PETCO_2$-tracing indicates 46 mmHg. Note the immediate increase in Pes and Pdi tidal pressure swings when PAV is terminated (arrow).

Table 3. Changes of pressures with PAV.

	Control 1	PAV	Control 2	p value (ANOVA)
PEEPi	0.32 + 0.18	0.17 + 0.08	0.35 + 0.09	NS
PTPdi	42.49 + 13.46	17.61 + 8.82*	41.32 + 11.10	<0.05
PTPdi/V'E	1.76 + 0.60	0.78 + 0.39*	1.78 + 0.53	<0.05

Definition of abbreviations: PEEPi = dynamic positive end-expiratory pressure (kPa); PTPdi = transdiaphragmatic pressure-time product calculated per minute (kPa*s); PTPdi/VT = transdiaphragmatic pressure-time product calculated per minute ventilation (kPa*s/L).
* Significant difference from control 1 and control 2.
Values are mean + SD for 6 subjects.

tilation-induced hypocapnia. Instead, our results indicate that non-chemical neuromechanical mechanisms are responsible for this effect.

Critique of Methods

A closer insight into motor output of the respiratory centre might have been obtained by assessment of surface or esophageal electromyographic (EMG) activity. We used pressure measurements instead, because exact quantification of the EMG-signal is difficult and smaller differences might not be detectable with this method. It has previously been shown that the transdiaphragmatic pressure-time product gives a good estimation of the oxygen cost of breathing [1, 11].

Using Pes and Pdi to gain a valid comparison of respiratory activity under different experimental conditions is linked to several prerequisites. First, during increased ventilatory demand, i.e. physical activity or CO_2-stimulated breathing, the expiratory and inspiratory muscles might share mechanical inspiration and changes in Pes might overestimate inspiratory muscle activity. In contrast, Pdi in this situation gives exact information of diaphragmatic motor output. Second, changes in Pes and Pdi reflect muscle activity only at comparable end-expiratory lung volumes (EELV). Since we did not measure lung volumes during the different experiments, our results might be incorrect if mechanical ventilation would have influenced EELV. Specifically, the unloading effect of PAV would have been overestimated, if EELV was lower during mechanical ventilation compared to spontaneous breathing. Indirect insight into the level of EELV is available by measurement of PEEPi. PEEPi reflects the elastic recoil pressure when EELV is larger than functional residual capacity at end-expiration. In fact, we observed increased levels of PEEPi during CO_2-stimulation and PEEPi was slightly reduced with PAV. PEEPi was probably induced by the expiratory resistance of the ventilatory equipment. Alternatively, activation of the expiratory muscles might have led us to overestimate PEEPi [13]. However, from the Pga tracings we observed no expiratory muscle activity. If the lower PEEPi during PAV reflects a decrease of EELV, we might have overestimated respiratory muscle unloading to some extent. The decrease in PEEPi however, was not significant. Because VT and breathing pattern were unchanged during the experiment, it is more likely that EELV also did not significantly change.

Our experiment was performed during wakefulness. Therefore, behavioural influences might have influenced our results. Although we cannot rule out this possibility, a more than marginal effect is unlikely for the following three reasons. First, all subjects were familiar with the experimental set up and had taken part in at least one experiment with non-invasive PSV or PAV before. They had been teached to relax during mechanical ventilation, thus avoiding voluntary hyperventilation if possible. Second, inspection of the pres-

sure curves revealed no active interference with the spontaneous breathing rhythm. Third, all calculations were derived from the end of 15-min runs. This long duration of each experiment makes it likely that steady state was achieved in all experiments.

With PAV $PETCO_2$ was slightly, but not significantly reduced by 1.2 mm Hg. CO_2-reduction might have reduced respiratory activity, indicating a chemical influence on respiratory motor output. While we cannot rule out, that this mechanism has played a certain role, we think it unlikely to be of more than marginal importance compared with non-chemical influences. First, diaphragmatic muscle unloading by 57 percent cannot be explained by the $PETCO_2$-reduction of only 1.2 mmHg alone. Second, the reduction of CO_2 with PAV was not significant. One might argue that the lack of significance is a consequence of the small number of experiments. The effect, however, was not consistent at all. In fact in half of the experiments $PETCO_2$ was slightly increased rather than decreased. In contrast respiratory activity was invariably decreased in all subjects.

Effect of PAV on Inspiratory Muscle Activity

The main finding of this study is, that with PAV the respiratory muscles were significantly unloaded, while tidal ventilation and breathing frequency was unchanged. From former investigations it was unclear how the respiratory control system would respond to the applied pressure when persisting inspiratory drive beyond a "triggering phase" is necessary to activate the PAV-ventilator. Principally two reactions are possible: an inhibition of muscle activity at a constant level of ventilation or a persistent level of respiratory drive with consecutive hyperventilation.

Two former investigations performanced in resting normal volunteers during wakefulness have shown that inspiratory assistance with PAV and PSV increases ventilation [6, 10]. Because arterial CO_2 was subsequently reduced, non-chemical effects on the respiratory centre are difficult to measure. Behavioural effects have been put forward to explain the hyperventilation during such experiments [23]. In contrast, during sleep or when ventilatory demand is increased during exercise or CO_2-stimulation, behavioural effects play a minor role and the respiratory centre gives a higher priority to muscle rest [7, 13, 18]. Wilson et al. [23] performed respiratory muscle unloading with assist control ventilation at increased tidal volume in sleeping humans. $PETCO_2$ was held constant by adding CO_2 to the inspirate. From the observation that respiratory motor output was decreased and subsequent hypocapnia did not further inhibit respiratory muscle activity, the authors concluded that non-chemical mechanisms must have been involved in the reduced respiratory muscle activity. The ventilatory mode used in this experiment limits the subjects' influence to control for tidal volume or timing of the breathing cycle. The authors hypothesized that the increased VT might be one mechanism responsible for the observed effect. In contrast, results of our study indicate that increased VT is no prerequisite to rest the respiratory muscles. We found, that application of positive pressure within the level of spontaneous VT was sufficient to inhibit respiratory motor output.

Faroux et al. [5] investigated the effect of respiratory muscle unloading in awake volunteers. Although they used a different ventilatory mode and a different experimental design, conclusions of this study are in line with our results. With PSV ventilation was increased and CO_2 was reduced. Respiratory muscle activity was consecutively reduced as well. When inspiratory CO_2 was increased up to the $PETCO_2$-level of unsupported spontaneous breathing, transdiaphragmatic pressure as well as diaphragmatic EMG-activity did not change. If a chemical mechanism had played the dominating role in respiratory muscle rest, one would have expected a subsequent increase in respiratory motor output along with the CO_2-increase. Because in this experiment VT was doubled with PSV, the exact comparison of respiratory motor output between spontaneous and supported breathing is difficult. Respiratory mechanics might have changed with the increased volume. Inductive plethysmography however revealed no changes in EELV. In our experiment we used PAV instead of PSV, because PAV might have advantages in matching the subjects ventilatory demand with the mechanical supply. Both modes of mechanical ventilation, though triggered by the subject, differ in one important respect. PSV provides a defined amount of ventilatory assist once the ventilator is activated. Any inspiratory effort beyond the triggering phase does not affect the amount and characteristics of pressure generated by the machine. Ideally inspiratory effort could be reduced to zero after the ventilator has started inspiratory assist. It has been shown earlier, however, that neural drive may persist throughout a considerable part of inspiration, thus reducing the work of breathing much less than might be expected [12]. With PAV on contrary persisting inspiratory drive is necessary to trigger the ventilator [25]. Once inspiratory muscle activity stops, pressure support generated by the machine also stops. The responding pressure supply should thus closely reflect the subjects demand in timing and flow. Only the proportion, by which the machine responds to subject's demands, is preset before. This close feedback system has the potential advantage to better match the subjects demands than other modes of assisted ventilation. Theoretically this might also reduce the likelihood of machine-driven hyperventilation because ventilatory support remains under the subjects control, even when respiratory muscles are unloaded to a considerable degree. The study cited above, however indicates, that with PSV the physiological effects upon respiratory drive are comparable to PAV. This is also indicated by a former study of Poon et al. [18]. During moderate exercise with minute ventilation comparable to our study, inspiratory drive measured by P01 was reduced with PSV, whereas ventilation was not significantly increased.

These results are contrasted by a recent study in awake volunteers by Georgopoulos et al. [9]. During Read CO_2 rebreathing tests they investigated the effect of PAV on respiratory muscle activity. PAV induced an increase of VT at all CO_2 levels, while total pressure of

the respiratory muscles and Pdi was not reduced. In contrast, in our experiment no supplementation of CO_2 was necessary to control for confounding chemical effects induced by machine-driven hyperventilation; with PAV VT and breathing pattern did not change. Our experiment differs in two aspects from the former study. It is unlikely that the different ways of inducing hypercapnia – Read rebreathing technique vs. steady state – is responsible for the different results. Of importance, however, may be the different ventilator-subject interfaces. Georgopoulos et al. used a mouthpiece while we applied PAV by means of a nasal mask. Supported ventilation via nose-mask may inhibit ventilatory drive by stimulation of nasal cold receptors [3]. This mechanism might explain why in our experiment PAV induced no hyperventilation. While Georgopolos et al. conclude, that chemical influences are the main reason for respiratory muscle unloading, a recent study by Shashar et al. [21] has found results comparable to our study. When normal subjects were exposed to different levels of inspiratory CO_2, ventilatory support effectively reduced diaphragmatic muscle activity, while breathing pattern and endtidal CO_2 was unchanged. In this experiment, pressure output of the ventilator was proportional to transdiaphragmatic pressure generated by the subject during inspiration.

While the results of Shasar et al. [21] as well as our data clearly speak in favour of neuromechanical inhibition induced by positive pressure on the airways, they do not elucidate the exact physiological pathway. Increasing flow through the upper airways might have produced an inhibitory response. Alternatively, thoracic displacement imposed by PAV might have affected peripheral mechanoreceptors in the lung parenchyma, airways or chest wall [22]. No changes of VT or breathing pattern were required to inhibit respiratory motor output. In addition, we have observed that when ventilatory assist was removed, the first unsupported breath increased respiratory muscle activity nearly to the level of the following breaths (Fig. 2). This demonstrates a very quick response of the respiratory controller to changes in mechanical support.

Clinical Implications

This study shows that with non-invasive PAV ventilation in healthy subjects remains well under the subject's control, while respiratory muscles are effectively unloaded. Our experimental design stimulates breathing by CO_2 inhalation. However, CO_2-stimulated breathing differs from respiratory disease. Different elastic and resistive loads may be imposed on the respiratory system, different receptors activated and different breathing strategies adopted by the patient. The observations made in this investigation, therefore, may not be seen in patients with respiratory disease, specifically if neuroventilaty coupling is not intact or if patient-ventilator interaction is impaired by leaks around the nose masc. Also, the impact of PAV may not be easily predictable since the patient has so much control over the ventilatory pattern. Further clinical studies are necessary to learn in which patients PAV is safe and if it is superior to traditional modes of partial ventilatory assist in terms of compliance, muscle unloading and alveolar ventilation.

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