Clinical Assessment of Auto-positive End-expiratory Pressure by Diaphragmatic Electrical Activity during Pressure Support and Neurally Adjusted Ventilatory Assist

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ABSTRACT

Background: Auto-positive end-expiratory pressure (auto-PEEP) may substantially increase the inspiratory effort during assisted mechanical ventilation. Purpose of this study was to assess whether the electrical activity of the diaphragm (EAdi) signal can be reliably used to estimate auto-PEEP in patients undergoing pressure support ventilation and neurally adjusted ventilatory assist (NAVA) and whether NAVA was beneficial in comparison with pressure support ventilation in patients affected by auto-PEEP.

Methods: In 10 patients with a clinical suspicion of auto-PEEP, the authors simultaneously recorded EAdi, airway, esophageal pressure, and flow during pressure support and NAVA, whereas external PEEP was increased from 2 to 14 cm H_2O. Tracings were analyzed to measure apparent "dynamic" auto-PEEP (decrease in esophageal pressure to generate inspiratory flow), auto-EAdi (EAdi value at the onset of inspiratory flow), and ID_{EAdi} (inspiratory delay between the onset of EAdi and the inspiratory flow).

Results: The pressure necessary to overcome auto-PEEP, auto-EAdi, and ID_{EAdi} was significantly lower in NAVA as compared with pressure support ventilation, decreased with increase in external PEEP, although the effect of external PEEP was less pronounced in NAVA. Both auto-EAdi and ID_{EAdi} were tightly correlated with auto-PEEP ($r^2 = 0.94$ and $r^2 = 0.75$, respectively). In the presence of auto-PEEP at lower external PEEP levels, NAVA was characterized by a characteristic shape of the airway pressure.

Conclusions: In patients with auto-PEEP, NAVA, compared with pressure support ventilation, led to a decrease in the pressure necessary to overcome auto-PEEP, which could be reliably monitored by the electrical activity of the diaphragm before inspiratory flow onset (auto-EAdi). **(Anesthesiology 2014; 121:563-71)**

DURING controlled or assisted ventilation, alveolar pressure is expected to equalize airway pressure at end-expiration. This is not the case in the presence of auto-positive end-expiratory pressure (auto-PEEP), which is defined as the alveolar pressure (above the set PEEP) at the end of a normal expiration.[1,2] Auto-PEEP can be caused by: (1) insufficient time for exhalation relative to the respiratory system's time constant, which causes gas trapping (dynamic hyperinflation); (2) airflow limitation with small airways collapse below a threshold pressure during expiration.[3] Auto-PEEP is a typical finding in patients with chronic obstructive pulmonary disease,[4] but its presence has been shown in a large proportion of ventilated patients.[5]

During assisted spontaneous breathing, auto-PEEP may represent a substantial workload for the patient: after the initiation of an inspiratory effort, the gas will not flow from the airways to the alveoli until the pressure generated by inspiratory muscles overcomes auto-PEEP. Of note, this effort is isometric and entirely wasted in terms of ventilation, resulting in increased energy expenditure of the breathing muscles.[6] Moreover, the presence of auto-PEEP will worsen the patient–ventilator interaction by affecting the ventilator's

What We Already Know about This Topic

- Auto-positive end-expiratory pressure may increase the inspiratory effort during assisted mechanical ventilation; its assessment can be obtained by measuring esophageal pressure.

What This Article Tells Us That Is New

- In 10 patients with auto-positive end-expiratory pressure, neurally adjusted ventilatory assist ventilation and pressure support ventilation were compared during positive end-expiratory pressure trials. The pressures required to overcome auto-positive end-expiratory pressure were significantly less with neurally adjusted ventilatory assist than with pressure support ventilation and could be reliably assessed by diaphragmatic electrical activity monitoring in comparison with esophageal pressure.

Corresponding article on page 447. This work was presented, in part, at the 25th Annual Congress of the European Society of Intensive Care Medicine, Lisbon, Portugal, October 13–17, 2012.

Submitted for publication August 7, 2013. Accepted for publication April 24, 2014. From the Department of Health Science, University of Milan-Bicocca, Monza, Italy, and Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy (G.B., N.P., A.P.); Department of Health Science, University of Milan-Bicocca, Monza, Italy (A.C., M.T., S.A.M., T.M.); and Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy (G.G.).

 Anesthesiology 2014; 121:563-71

efficiency to detect patient's inspiratory efforts. However, since the ventilator is controlled by the electrical activity of the diaphragm (EAdi) rather than by airflow and pressure signals during neurally adjusted ventilatory assist (NAVA), we hypothesized that ventilator triggering would occur earlier in response to patient's demand leading to an improved patient–ventilator synchrony as compared with pressure support ventilation (PSV) in patients affected by auto-PEEP.

Accurate estimation of auto-PEEP would be clinically useful for diagnostic purposes and for selecting appropriate ventilatory settings: if auto-PEEP is due to airflow limitation, the application of an external PEEP (PEEPe) may decrease the pressure gradient between the alveoli and the airways during expiration,[7] thus reducing the triggering effort and improving patient–ventilator synchrony.[8,9] During assisted spontaneous breathing, auto-PEEP is not easy to measure at the bedside: the use of an end-expiratory occlusion (the reference technique during controlled ventilation)[8] is not always suitable due to incomplete patient's relaxation. A reliable method, although not frequently applied in the clinical practice, is represented by esophageal pressure (Pes) measurement: the pressure decrease between the initiation of the effort and the onset of the airflow equals "dynamic" auto-PEEP.[10,11]

The electrical activity of the crural diaphragm (EAdi), a measurement available on one commercial ventilator, constitutes the temporo-spatial summation of the action potentials from the recruited motor units and it is linearly related to the pressure generated by the respiratory muscles, thus allowing its robust estimation.[12,13] We reasoned that, because Pes is used to estimate the pressure generated by the respiratory muscles to overcome auto-PEEP, the same measurement could be obtained by means of EAdi during PSV and NAVA.

Materials and Methods

We prospectively enrolled 10 intubated patients undergoing PSV, with a clinical suspicion of auto-PEEP (based on the clinical history and/or findings on the ventilator waveform, such as nonlinear expiratory flow tracings on the volume axis,[14] during reduction of PEEPe). Exclusion criteria were the presence of air leaks, hemodynamic instability requiring vasoactive drugs, Richmond Agitation Sedation Score greater than 1, and contraindication to nasogastric tube replacement.

Data Acquisition

Study protocol was approved by the local ethical committee (San Gerardo Hospital, Monza, Italy) and informed consent was obtained from the patients following its policies.

After enrollment, a nasogastric tube equipped with NAVA electrodes (Maquet, Solna, Sweden) and an esophageal balloon (Cooper Surgical, Trumbull, CT) were positioned, if not already present. The NAVA catheter was connected to a Servo-I ventilator (Maquet) sending the EAdi signal to a first personal computer. This first personal computer, by means of dedicated software (Labview; National Instruments, Austin, TX) acquired waveforms of airway pressure, airflow and EAdi and returned them as analog outputs by a digital-to-analog converter (DAQcard; National Instruments, Houston, TX) to a second personal computer.

Two air-filled pressure transducers (T100209A; Edwards Lifesciences, Irvine, CA) were connected to the airway opening and to the esophageal balloon, and their signals were acquired by a data acquisition system (Powerlab; ADInstruments, Colorado Springs, CO) on the second personal computer which recorded, with a sampling frequency of 100 Hz, all the aforementioned waveforms. Data were continuously recorded during the study for offline analysis.

Study Protocol

At the beginning of the protocol, we checked and, if necessary, corrected the position of the nasogastric tube according to the manufacturer's instructions for the EAdi signal (*i.e.*, inserting or retracting the nasogatric tube by a few centimeters to obtain a visible signal arising from electromyogram, in the most central part of the electrodes array) and to the standard calibration procedure of Pes.[15] Patients remained in PSV, PEEPe was progressively increased, in steps of 2 cm H_2O, from 2 to 14 cm H_2O. Each level was maintained for 3 min. PEEP was then set back to the baseline clinical level for 3 min; patients were switched to NAVA with a level aiming at similar peak pressures as those observed in PSV at baseline PEEPe. The PEEP trial was then repeated with the same levels previously indicated.

Data Analysis

Data were analyzed offline. At first, we computed the elastance of the chest wall as the difference between end-inspiratory and end-expiratory Pes divided by tidal volume, during a short phase of controlled ventilation. Muscle pressure (Pmusc) was then calculated as the difference between Pes (filtered to damp the heart artifacts) and the chest wall elastic recoil curve (equal to the instant-by-instant product of the volume above end-expiration by chest wall elastance).[14]

For each of the seven PEEP levels applied both during PSV and NAVA, we analyzed 20 tidal volumes avoiding waveform sections of poor signal quality (*e.g.*, cough, presence of peristaltic waves on the esophageal pressure signal). In each patient, we also measured the Pmusc/EAdi index as the ratio between airway pressure decrease and the corresponding EAdi value during one end-expiratory occlusion, as previously reported[13]: it indicates the pressure developed by the inspiratory muscles per each 1 μV of EAdi.

For each tidal volume, we defined the following variables (fig. 1):

- Apparent auto-PEEP: difference of Pes between end-expiration and at the onset of inspiratory flow. It is important to underline that this method ("Pes counterbalance") actually measures the esophageal pressure change required to overcome the auto-PEEP and trigger an airway pressure triggered PSV breath. The term "apparent" was thus introduced to underline the concept that, in NAVA, due to the use of EAdi signal this

might result in an earlier trigger activation. In NAVA, the apparent auto-PEEP will thus only be a measure of the effort necessary to activate the trigger but, at variance with PSV, this will not necessarily indicate the end-expiratory alveolar pressure above PEEPe.

- auto-EAdi: value of EAdi at the onset of inspiratory flow
- auto-$PEEP_{EAdi}$: EAdi-based calculation of auto-PEEP, as the product of auto-EAdi × Pmusc/EAdi index/1.5.[13] The 1.5 correction was introduced to account for the fact that during tidal ventilation, the "dynamic Pmusc/EAdi index" is about 1.5-fold smaller than the "occlusion Pmusc/EAdi index," measured during one end-expiratory hold.[13]
- ID_{EAdi}: inspiratory delay between the onset of EAdi activity and the onset of inspiratory flow.
- $EAdi_{peak}$: highest EAdi value observed during inspiration.

Statistical Analysis

The sample size was based on previous similar physiological studies.[13] The effects on the different variables of the two interventions performed in the study, that is, the change of the ventilatory mode (NAVA *vs.* PSV) and of the PEEPe, were tested by a two-way ANOVA for repeated measures in which the ventilatory mode and PEEPe were used as factors; the result of the interaction was used to understand whether the effect of one factor was affected by the level of the other factors (*e.g.*, if the response to PEEPe was different depending on the ventilatory mode applied). No *post hoc* analysis was performed. Because one patient did not tolerate the 14 cm H_2O PEEPe step, the 2 of 133 (1.5%) missing values were imputed to perform the ANOVA by the SPSS expectation-maximization algorithm (SPSS 19.0; IBM, Chicago, IL), using the PEEP variable as predictor. Bland–Altman analysis was used to compare the agreement between apparent auto-PEEP and auto-$PEEP_{EAdi}$, taking into account that each subject contributes with multiple values (MedCalc 13.1.2; MedCalc Software BVBA, Ostend, Belgium). The ANOVA was also repeated excluding the 14 cm H_2O step, obtaining similar results. Correlation between variables was assessed by linear regression. A level of P value less than 0.05 was considered as statistically significant.

Results

The main characteristics of the study population are detailed in table 1. Several patients presented history for chronic obstructive pulmonary disease (50%) and four of them were admitted to the intensive care unit due to an exacerbation of this condition. All patients uneventfully completed the study protocol, except for one patient who did not tolerate the 14 cm H_2O PEEP step due to hypotension.

Effects of Ventilatory Mode and PEEPe on Apparent Auto-PEEP

Figure 2 shows the behavior of apparent auto-PEEP (fig. 2A), auto-EAdi (fig. 2B), and ID_{EAdi} (fig. 2C) at different levels of PEEPe during PSV and NAVA. Apparent auto-PEEP was higher in PSV than in NAVA ($P < 0.05$) and it declined in both modes with increasing PEEPe ($P < 0.001$): the effect of PEEPe was more pronounced in PSV than in NAVA (interaction $P < 0.001$). Auto-EAdi had a similar behavior, being significantly lower in NAVA than PSV ($P < 0.001$), decreasing with increasing PEEPe ($P < 0.05$) and with a significant interaction between PEEPe and ventilatory mode ($P < 0.001$). Also, the ID_{EAdi} was higher in PSV than in NAVA ($P < 0.001$), and it decreased with increasing PEEPe ($P < 0.001$) similarly between the two ventilatory modalities (interaction: $P = 0.451$).

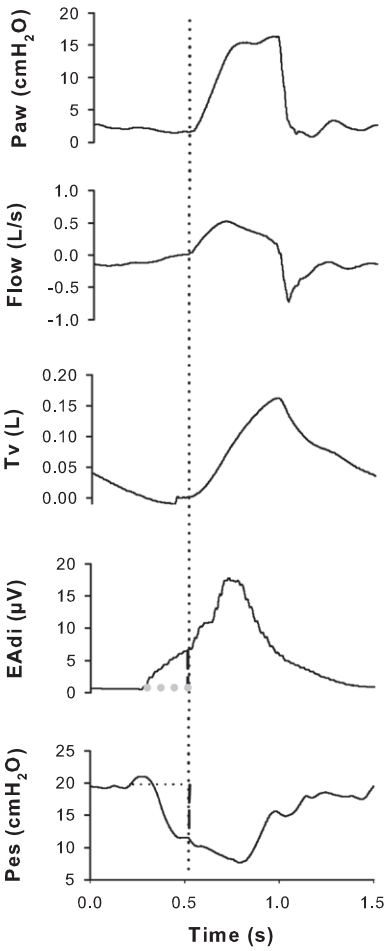

Fig. 1. Example of airway pressure (Paw), airflow (flow), volume (Tv), electrical activity of the diaphragm (EAdi), and esophageal pressure (Pes) recorded during pressure support ventilation. Auto-positive end-expiratory pressure was defined as the deflection of esophageal pressure at the time of the flow onset (*vertical dashed line* on the Pes tracing) from the Pes baseline (*horizontal dotted line* on the Pes tracing, corresponding to approximately 8 cm H_2O in this example). In analogy, intrinsic EAdi (auto-EAdi) was defined as the value of EAdi at the onset of the inspiratory airflow (*vertical dashed line* on the EAdi tracing corresponding to approximately 7 μV in this example). Inspiratory delay was defined as the temporal delay between the onset of EAdi activity and the onset of inspiratory flow (*horizontal dotted line* on the EAdi tracing corresponding to approximately 200 ms in this example).

Table 1. Clinical Data of the Patient Population

Age	74 (75–78)
SAPS II	47 ± 14
Male, n (%)	4 (40%)
Previous pulmonary conditions, n (%)	
COPD	5 (50%)
Active smoke	2 (20%)
Silicosis	1 (20%)
None	2 (20%)
ICU admission diagnosis, n (%)	
COPD exacerbation	4 (40%)
Sepsis	3 (30%)
Postoperative	2 (20%)
Trauma	1 (10%)
ICU survivors, n (%)	8 (80%)
Pao_2/FIo_2 ratio (mmHg)	222 ± 62
$Paco_2$ (mmHg)	52.5 ± 14.8
Clinical PEEPe (cm H_2O)	9 ± 3
Clinical pressure support (cm H_2O)	4 (6–12)
Days of intubation	4 (6–8)
Respiratory system compliance (ml/cm H_2O)	43 ± 15
Respiratory system resistance (cm H_2O l^{-1} s^{-1})	17 ± 4
Respiratory system time constant (s)	0.71 ± 0.30

Data are represented as median (range interquartile) or mean ± SD.

COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; PEEPe = extrinsic positive end-expiratory pressure; SAPS = Simplified Acute Physiology Score.

Table 2 reports main ventilatory variables during the study. Tidal volume increased (effect of PEEPe $P < 0.01$) with increasing PEEPe, similarly between PSV and NAVA (effect of interaction $P = 0.920$). The patient's effort decreased, as indicated by the decrease in $EAdi_{peak}$ (effect of PEEP $P < 0.01$, ventilatory mode $P = 0.194$, interaction $P < 0.05$), mirroring the behavior of Pmusc. The decrease of $EAdi_{peak}$ at increasing PEEPe was largely due to the progressive decrease of apparent auto-PEEP, as indicated by the tight correlation between the decrease in $EAdi_{peak}$ and both apparent auto-PEEP (fig. 3A) and auto-EAdi (fig. 3B). Although in PSV the driving pressure of the ventilator, by definition, was constant irrespective of the set PEEPe, in NAVA the inspiratory pressure increased at lower PEEPe as a consequence of the increased EAdi, providing a greater assistance to the patient ($P < 0.05$). Respiratory rate decreased at increasing levels of PEEPe ($P < 0.001$), with no difference between NAVA and PSV (table 3 also reporting inspiratory and expiratory times).

The presence of a significant auto-PEEP during NAVA was consistently associated with a typical shape of the airway pressure, namely a sudden increase in airway pressure after the neural trigger threshold, followed by a phase of decline and a subsequent rise (fig. 4); the underlying mechanism is discussed in the figure 4.

EAdi-based Assessment of Auto-PEEP

As shown in figure 5A, on average, apparent auto-PEEP was tightly correlated with auto-EAdi both in PSV ($r^2 = 0.94$; $P < 0.001$) and, with a steeper relationship, in NAVA ($r^2 = 0.90$; $P < 0.001$). Moreover, auto-PEEP was tightly correlated with ID_{EAdi} (fig. 5B) both in PSV ($r^2 = 0.75$; $P < 0.01$) and in NAVA ($r^2 = 0.72$; $P < 0.01$). At individual patient analysis, we found a highly significant correlation

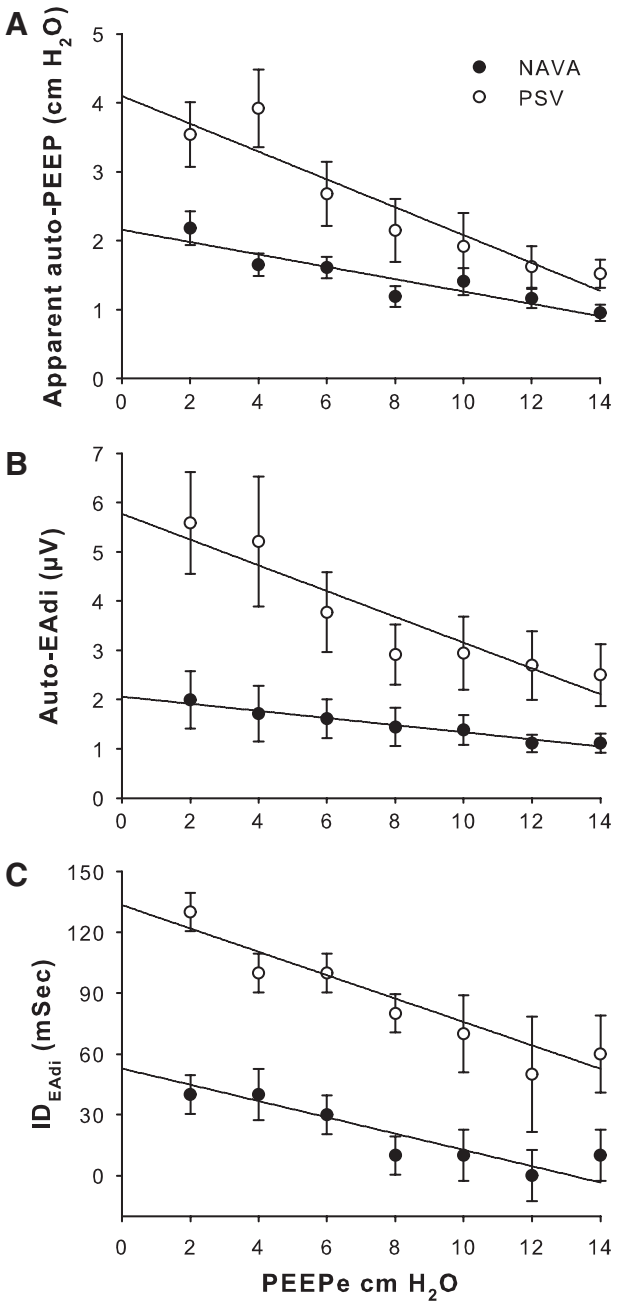

Fig. 2. Effect of extrinsic positive end-expiratory pressure (PEEPe) and ventilatory mode on auto-PEEP (*A*), value of the electrical activity of the diaphragm at the time of the flow onset (auto-EAdi, *B*), and delay between onset of the electrical activity of the diaphragm and flow (ID_{EAdi}, *C*). All the three variables were lower during neurally adjusted ventilatory assist (NAVA) than during pressure support ventilation (PSV) and decreased with the increase in PEEPe. It can be noticed that the decrease was less steep in NAVA as compared with PSV (see "Effects of Ventilatory Mode and PEEPe on Apparent Auto-PEEP" section in text for statistics).

Table 2. Main Ventilatory Variables during the Study

		PEEPe (cm H_2O)							ANOVA *P* Values		
		2	4	6	8	10	12	14	PEEPe	Mode	Interaction
Vt (ml)	NAVA	0.40±0.17	0.40±0.15	0.42±0.15	0.39±0.18	0.43±0.17	0.45±0.18	0.42±0.16	<0.001	0.464	0.920
	PSV	0.36±0.17	0.35±0.18	0.39±0.17	0.41±0.17	0.42±0.16	0.41±0.15	0.40±0.15			
Peak EAdi (μV)	NAVA	16.7±9.1	14.3±8.5	14.1±7.3	12.8±6.5	13.4±6.3	11.8±5.3	12.1±5.3	<0.001	0.194	0.048
	PSV	20.9±12.1	22.4±13.1	18.7±11.9	15.2±9.6	16.6±9.5	12.7±6.1	13.8±7.3			
Peak Pmusc (cm H_2O)	NAVA	10.0±3.9	8.1±3.8	7.7±3.5	6.8±3.4	6.7±3.6	6.2±3.8	4.6±1.9	<0.001	0.279	0.002
	PSV	10.4±3.2	11.9±4.7	9.9±4.9	8.0±3.6	7.4±3.1	6.2±2.7	6.2±2.6			
Baseline EAdi (μV)	NAVA	0.48±0.21	0.45±0.15	0.48±0.21	0.43±0.10	0.47±0.13	0.47±0.19	0.44±0.15	0.028	0.156	0.04
	PSV	0.82±0.54	0.89±0.83	0.74±0.59	0.5±0.19	0.56±0.32	0.46±0.25	0.47±0.24			
P0.1 (cm H_2O)	NAVA	3.5±1.7	2.7±0.9	2.8±1.2	2.4±0.5	2.3±0.6	2.0±0.9	2.0±1.1	<0.001	0.619	0.442
	PSV	3.6±1.7	3.1±1.8	2.7±1.2	1.8±0.8	2.1±1.0	2.1±1.2	1.9±1.5			
Driving Pr. (cm H_2O)	NAVA	12.0±5.3	10.7±5.8	10.0±5.1	9.3±4.7	9.8±5.3	9.1±5.9	9.2±4.9	0.103	0.014	0.03
	PSV	7.1±4.2	7.2±4.6	7.3±4.5	7.3±4.4	7.2±4.4	7.2±4.6	7.4±4.5			

Data are expressed as mean ± SD.

Driving pr = diving pressure (difference between PEEPe and peak inspiratory airway pressure); EAdi = electrical activity of the diaphragm; NAVA = neurally adjusted ventilatory assist; PEEPe = estrinsic positive end-expiratory pressure; Pmusc = muscle pressure; PSV = pressure support ventilation; Vt = tidal volume.

between auto-PEEP and auto-EAdi (average $r^2 = 0.68 \pm 0.17$; $P < 0.05$ for all patients) and between auto-PEEP and ID_{EAdi} (average $r^2 = 0.51 \pm 0.12$; $P < 0.05$ for all patients).

Finally, the conversion of auto-EAdi to auto-$PEEP_{EAdi}$ provided a clinically acceptable estimate of apparent auto-PEEP measured with esophageal pressure during PSV and NAVA with a 95% CI between +0.99 and −2.1 cm H_2O (fig. 6).

Discussion

The main findings of this article can be summarized as follows: in a cohort of patients with a clinical suspicion of gas trapping, the EAdi signal provides a promising tool for monitoring the presence of auto-PEEP and the effects of the application of an PEEPe, which appears comparable to Pes. During NAVA, the effort necessary to overcome auto-PEEP was lower than during PSV, and it was less affected by the decrease of PEEPe.

Auto-PEEP is commonly defined as the pressure (above PEEPe) in the alveoli at the end of a passive expiration. Detecting auto-PEEP, and ideally quantitating it, could be clinically relevant for diagnostic purposes (*e.g.*, in difficult-to-wean patients) and to guide the application of PEEPe, which, in some cases, may counterbalance auto-PEEP. Nevertheless, the measurement of auto-PEEP during assisted ventilation represents a challenge because the end-expiratory airway occlusion method[8] is not always applicable due to the risk of incomplete relaxation of the patients.[2] A more reliable option is to measure the "dynamic" auto-PEEP[10] as the deflection in Pes from the beginning of an inspiratory effort to the onset of inspiratory flow: what is actually measured with this approach is the Pmusc necessary to counterbalance auto-PEEP, decreasing alveolar pressure below the airway pressure, and generating inspiratory flow. As stated, at

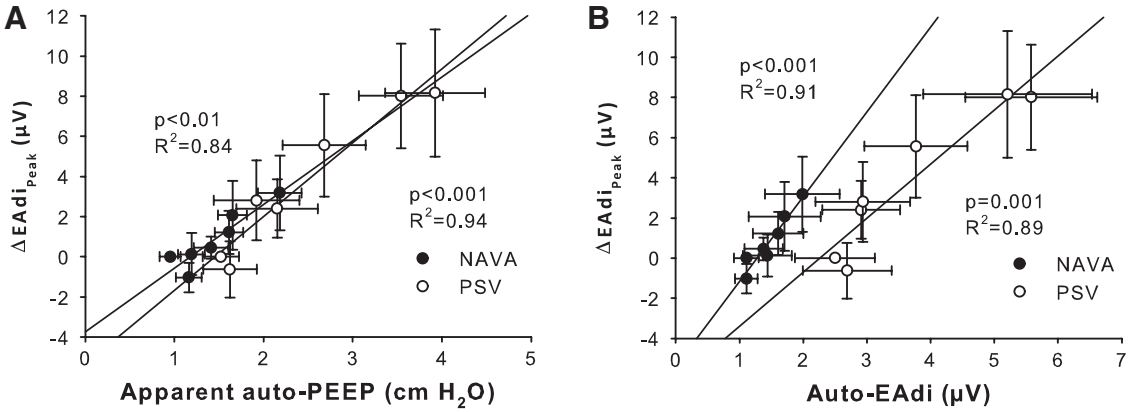

Fig. 3. The graphs show the correlation between the change in peak electrical activity of the diaphragm (EAdi) for each positive end-expiratory pressure (PEEP) level in comparison with 14 cm H_2O ($\Delta EAdi_{peak}$) and the respective changes in auto-PEEP (*A*) and in auto-EAdi (*B*). The highly significant correlation suggests that the observed decrease of peak EAdi was largely explained by the decrease of auto-PEEP (and thus of auto-EAdi), offered by the counterbalance of PEEPe. NAVA = neurally adjusted ventilatory assist; PSV = pressure support ventilation.

Table 3. Inspiratory and Expiratory Times

		PEEPe (cm H_2O)							ANOVA *P* Values		
		2	4	6	8	10	12	14	PEEPe	Mode	Interaction
RR (1/min)	NAVA	27 ± 12	26 ± 11	25 ± 11	25 ± 11	25 ± 11	23 ± 10	23 ± 10	<0.001	0.609	0.263
	PSV	26 ± 12	27 ± 12	25 ± 10	23 ± 10	23 ± 10	22 ± 9	22 ± 8			
Ti (s)	NAVA	0.82 ± 0.32	0.83 ± 0.30	0.86 ± 0.32	0.84 ± 0.30	0.87 ± 0.30	0.87 ± 0.28	0.88 ± 0.26	0.006	0.656	0.065
	PSV	0.76 ± 0.28	0.79 ± 0.30	0.81 ± 0.27	0.84 ± 0.22	0.92 ± 0.29	0.87 ± 0.20	0.86 ± 0.19			
Te (s)	NAVA	1.89 ± 1.13	2.02 ± 1.37	2.17 ± 1.56	2.11 ± 1.31	2.16 ± 1.58	2.23 ± 1.30	2.29 ± 1.34	0.299	0.249	0.474
	PSV	2.27 ± 1.98	2.09 ± 1.66	1.97 ± 1.01	2.26 ± 1.37	2.10 ± 1.13	2.25 ± 1.18	2.29 ± 1.22			

Data are expressed as mean ± SD.

NAVA = neurally adjusted ventilatory assist; PEEPe = estrinsic positive end-expiratory pressure; PSV = pressure support ventilation; RR = respiratory rate; Te = expiratory times; Ti = inspiratory times.

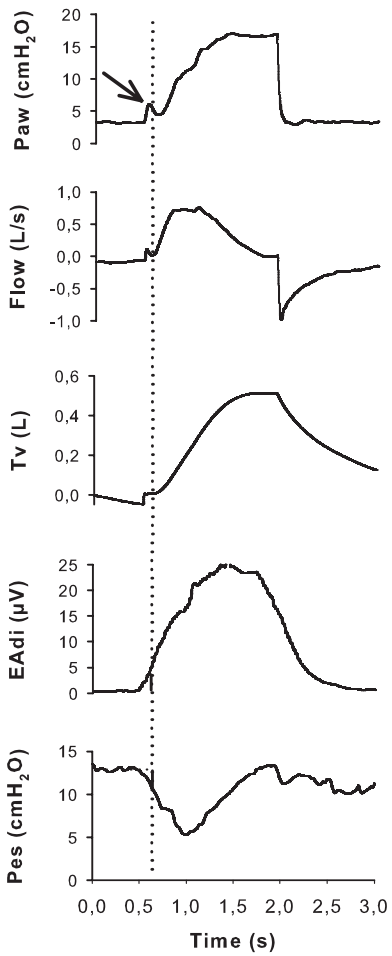

Fig. 4. Typical shape of the airway pressure (Paw) trace during neurally adjusted ventilatory assist (NAVA) in the presence relevant of auto-positive end-expiratory pressure (PEEP): when the triggering threshold is reached on the electrical diaphragm activity (EAdi), the ventilator closes the expiratory valve, causing, in the presence of auto-PEEP, an abrupt raise in Paw (*black arrow*). If the raise in Paw numerically exceeds the product of EAdi by NAVA level (*i.e.*, the level of assistance set on the ventilator during NAVA), the ventilator will deliver only a minimal flow (or none), resulting in a transient decrease of Paw; later, the increase of EAdi (and consequently of the EAdi by NAVA-level product) will cause a "normal" NAVA airway pressure inspiratory profile. Pes = esophageal pressure; Tv = Tidal volume.

variance from PSV, in NAVA the presence of the neural trigger prevents the need to fully counterbalance the auto-PEEP before activating the ventilator. For this reason, we used the term "apparent auto-PEEP," indicating that in NAVA this value indicates the effort spent before activation of the ventilator, but not necessarily the end-expiratory alveolar pressure above PEEPe.

Since previous works demonstrated that EAdi is proportional to Pmusc,[12,13,16,17] we reasoned that, in analogy with the Pes-based measurement of dynamic auto-PEEP, the EAdi level at the onset of inspiratory flow may be proportional to dynamic auto-PEEP (for this reason we termed it "auto-EAdi"). We thus tested this hypothesis, showing proportionality between dynamic auto-PEEP and both auto-EAdi and ID_{EAdi}; this relationship was present in all patients individually and, more strongly, at the level of the entire population. These results suggest that this approach, readily and simply applicable at the bedside, might allow a breath-by-breath monitoring of auto-PEEP; although Pes remains the standard method for Pmusc pressure measurement, our data show that EAdi might provide useful information appearing, at least in our hands, a more simple and less noisy equipment. Moreover, the variations of auto-EAdi and ID_{EAdi} at different PEEPe levels mirrored that of auto-PEEP, suggesting that auto-EAdi and ID_{EAdi} could be simply and readily used at the bedside to titrate PEEPe and to assess the effect of different therapeutic strategies. In our patients, the increase in PEEPe led to a significant decrease of auto-PEEP (and auto-EAdi), suggesting a predominant role of airflow limitation as compared with dynamic hyperinflation, although conflicting data exist on this matter.[18]

Our study has some limitations. Due to the rather complex experimental setup, we measured esophageal but not abdominal pressure. This limitation did not allow us to differentiate the presence of auto-PEEP from potential expiratory muscle activity. However, the evaluation of auto-EAdi should not be affected by the presence of active expiratory efforts representing the sole diaphragmatic muscular activity. Another limitation of the study is the relatively small sample size which is not uncommon in such studies focused on physiological variables. Moreover, we did not randomize

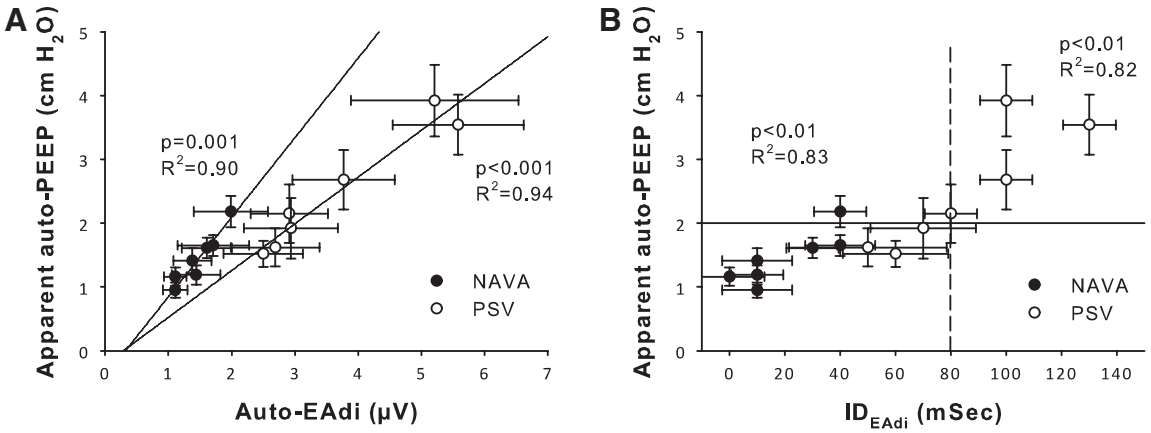

Fig. 5. The graphs show the tight correlation existing between auto-positive end-expiratory pressure (auto-PEEP) and value of the electrical activity of the diaphragm at the time of the flow onset (auto-EAdi) (*A*) and between auto-PEEP and inspiratory delay measured by electrical activity of the diaphragm at the time of the flow onset (ID_{EAdi}, *B*). Each *point* represents the average of the values measured at one level of PEEPe in neurally adjusted ventilatory assist (NAVA, *filled symbols*) and in pressure support ventilation (PSV, *empty symbols*). In respect to *B*, it can be noticed that both in PSV and NAVA an ID_{EAdi} lower than 80 ms is usually associated with an auto-PEEP below 2 cm H_2O.

the order of PEEPe application, but we used a stepwise increase of PEEPe like other authors did.[18] As we compared overall trends in variables during changes of PEEPe, we are doubtful that randomization of PEEPe would have had relevant effects. In our patients, the inspiratory pressure swings in NAVA were higher in comparison with PSV. Despite our attempt of matching the level of assistance of the two ventilation modalities at the beginning of the study, the decrease in PEEPe led to an increased EAdi (increased patient's effort), leading, in turn, to an increased airway pressure swing in NAVA. This is intrinsic to NAVA technique, and thus we provide a comparison of the "overall" behavior of PSV and NAVA (including the ability of the latter technique to react to an increased effort of the patient).

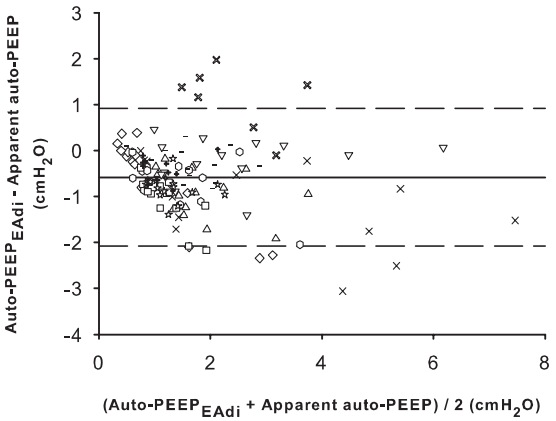

Fig. 6. Bland and Altman plot for the comparison between auto-positive end-expiratory pressure (auto-PEEP) measured by the esophageal pressure and by the diaphragmatic electromyogram (auto-$PEEP_{EAdi}$), by converting the electrical activity of the diaphragm at the time of the flow onset (auto-EAdi) to cm H_2O (95% CI between +0.99 and –2.1 cm H_2O). Each patient is indicated in the plot with a different symbol.

We might have changed the NAVA gain to obtain the same airway pressure swing at each PEEPe level but: (1) we would have introduced a confounder and (2) it was likely that the patients' EAdi would have further increased, leading to a consequent further airway pressure change. We believe that the effects on the main results of our article (*i.e.*, figs. 2–6) were marginally (if at all) affected by the different airway pressure swings, as our results are mainly focused on the early phase (onset) of inspiration.

In comparison with PSV, NAVA has been shown to ameliorate patient–ventilator synchrony in patients with acute respiratory failure.[19–21] To our knowledge, this is one the first reports directly comparing NAVA and PSV in a cohort of patients with a clinically relevant auto-PEEP. Spahija *et al.* compared PSV and a prototype of NAVA (at different levels) in a cohort of patients including a large fraction of patients with chronic obstructive pulmonary disease. They reported that the work necessary to activate the ventilator in NAVA was lower than in PSV and it was not affected by the level of assistance.[22] In that study, PEEPe was not modified, and the relationship between EAdi and the pressure necessary to activate the ventilator is not reported, preventing a comparison with the current study. Also Piquilloud *et al.*,[23] in a mixed population including about one third of patients with chronic obstructive pulmonary disease, showed an improved synchrony when NAVA was used, but neither esophageal pressure or auto-PEEP were measured.

In keeping with the literature, we measured auto-PEEP as negative Pes swing necessary to generate an inspiratory airway flow. We stick to this definition also in NAVA although in this ventilatory mode a positive EAdi swing will immediately trigger the ventilator to provide an inspiratory flow well before the Pmus has overcome the auto-PEEP. For this reason, during NAVA the "Pes counterbalance" method is not valid in measuring auto-PEEP as the actual end-expiratory alveolar

pressure due to gas trapping, but rather indicates only the pressure wasted before activation of the ventilator. Whether and by which mechanism NAVA also decreases gas trapping as compared with PSV should be addressed in a different study. NAVA however did not abolish entirely auto-PEEP (and auto-EAdi), and some effect of PEEPe was still evident. This apparent contradiction is reconciled considering that in NAVA the ventilator will drive airway pressure according to the product of EAdi and NAVA level. At the beginning of inspiration, this product will be small and will not exceed auto-PEEP with the consequent lack of a significant inspiratory flow. In extreme cases, this leads to a characteristic airway pressure shape (fig. 5). Although interesting from a physiological standpoint, we believe that the clinical impact of apparent auto-PEEP during NAVA is probably modest, rarely exceeding 2 cm H_2O even at lower levels of PEEPe. Taken together, these findings support the evidence that NAVA provides a better patient–ventilator synchrony than PSV in patients with a relevant auto-PEEP, especially at lower levels of PEEPe. This interpretation is supported by the observed increase of Pmusc and $EAdi_{peak}$ at lower PEEPe levels,[24] indicating a greater effort of the patient who was less pronounced in NAVA than in PSV. Further studies are required to elucidate whether NAVA, by improving patient–ventilator synchrony, would have an impact on patient outcomes such as a greater weaning success or a shorter duration of ventilation.

In conclusion, in a population of patients with auto-PEEP undergoing assisted ventilation, NAVA, compared with PSV, led to a decrease (but not to an abolishment) of the pressure necessary to overcome auto-PEEP, independent of the level of PEEPe. The electrical activity of the diaphragm (auto-EAdi) before the onset of the inspiratory flow provides a simple and reliable tool for continuously monitoring the presence of dynamic intrinsic PEEP at bedside.

Acknowledgments

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

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