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TITLE PAGE

Title

Assessment of airway driving pressure and respiratory system mechanics during Neurally Adjusted Ventilatory Assist

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MANUSCRIPT

To the Editor:

The airway driving pressure is the end-inspiratory plateau pressure (P_{plat}) minus total end-expiratory pressure (PEEP) (1). It is measured under no-flow conditions, by an end-inspiratory occlusion maneuver, which can be challenging during assisted ventilation. Nevertheless, measurement of driving pressure and respiratory system compliance (CPL_{RS}) has been described also during Pressure Support ventilation (PSV) (2). During Neurally Adjusted Ventilatory Assist (NAVA), the ventilator support is proportional to the electrical activity of diaphragm (EAdi) (3) and driving pressure is the sum of the pressures developed by the ventilator and the respiratory muscles. The former equals EAdi multiplied by a user-set gain ($cmH_2O/\mu Volt$), while the latter is a "hidden" pressure, which is not easily quantifiable during tidal ventilation. Aim of this study was to assess respiratory system mechanics during NAVA. First, we compared measures of CPL_{RS} between NAVA and PSV at similar tidal volumes (Vt), then we estimated the effects of different PEEP and ventilator assistance on driving pressure and on the pressure generated by the inspiratory muscles.

Methods

We studied a subset of patients enrolled in a trial evaluating NAVA in the early post-operative period after lung transplantation (ClinicalTrials.gov, NCT03367221), admitted to the Intensive Care Unit of

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Ospedale Maggiore Policlinico (Milan, Italy) from November 2017 to December 2018. The study was approved by the local Ethics Committee and all patients gave written informed consent.

Initially, patients were ventilated in PSV targeting a Vt of 4-8 ml/kg of predicted body weight. Once stabilized, patients were switched to NAVA, with a gain generating the same peak pressure as during PSV (baseline NAVA). Then, 4 support levels (PSV; baseline NAVA; 50% and 150% of baseline NAVA) were randomly applied at two PEEP levels (6 and 12 cmH_2O). At the end of each 20-minutes step (8 per patient), a 2-seconds end-inspiratory occlusion was performed (Figure 1) and repeated if not considered valid. Occlusions were considered valid when a stable and flat P_{plat} could be identified. The absence of EAdi activity and of positive airway pressure swings confirmed the absence of inspiratory and expiratory muscles activation. In two patients, this was further confirmed by esophageal pressure monitoring. Traces of airway pressure, flow and EAdi were recorded (Servo-Tracker, Getinge, Sweden) for offline analysis (LabChart, AD-Instruments, Colorado-Springs, CO). For each occlusion, the following variables were obtained: Vt, PEEP, P_{plat}, driving pressure, and CPL_{RS} (Vt/ΔP). In addition, for the occlusions performed during NAVA, we retrieved the peak EAdi ($EAdi_{peak}$), the pressure applied by the ventilator (P_{vent} = PEEP plus $EAdi_{peak}$ multiplied by gain) and the Pmusc index (PMI, a measure of the pressure developed by the inspiratory muscles, previously described during PSV (4) and calculated as P_{plat} minus P_{vent}) (Figure 1).

Data are presented as mean ± standard deviation or median and interquartile range. End-inspiratory occlusions with similar Vts (i.e., ratio of PSV and NAVA Vts between 0.8 and 1.2) were selected for linear regression and Bland and Altmann analysis to evaluate the agreement between measures of CPL_{RS} in the two ventilation modes at same PEEP level. A linear mixed model was applied, considering PEEP and NAVA level as fixed effects and subjects as random effect. A p value < 0.05 was deemed statistically significant. Statistical analysis was performed with JMP 14 (SAS, Cary, NC).

Results

Twelve patients (9 males, median age of 44 (24.75-58.5) years old) were studied. PSV and baseline NAVA levels were 3.5 (2-5.75) cmH_2O and 0.7 (0.2-1) cmH_2O/µVolt, respectively. Twenty-four end-inspiratory occlusions during PSV and 72 during NAVA were selected for the analysis. The maneuver was repeated in 4 and 23 cases during PSV and NAVA, to obtain a valid P_{plat}.

Vt during NAVA was similar to the corresponding value during PSV in 53 of 72 occlusions. Vt was 500 ± 183 and 541 ± 211 ml ($p < 0.01$), P_{plat} was 21.4 ± 6.0 and 21.9 ± 7.7 cmH_2O ($p = 0.06$) and CPL_{RS} 42.4 ± 8.0 and 43.3 ± 8.4 ml/cmH_2O ($p = 0.14$) during PSV and NAVA, respectively. Measurements of CPL_{RS} during NAVA and PSV showed significant correlation ($y = 2.05 + 0.97 * x$, $R^2 = 0.74$, $p < 0.001$), while the Bland and Altman analysis resulted in a clinically negligible systematic bias (1.1 ± 4.1 ml/cmH_2O) with 95% of difference scores within the limits of agreement (-6.8 and 9.1 ml/cmH_2O).

Table 1 shows the effects of changing NAVA and PEEP levels on respiratory parameters. Increasing the NAVA gain resulted in increased P_{vent} and decreased PMI, with no changes in Vt, $EAdi_{peak}$, P_{plat}, driving pressure and CPL_{RS}. At the higher PEEP level, Vt did not change, while $EAdi_{peak}$, driving pressure and PMI decreased and CPL_{RS}, P_{plat} and P_{vent} increased.

Discussion

In ARDS patients undergoing controlled ventilation, elevated driving pressure predicts mortality (5), possibly due to an increased risk of ventilator-induced lung injury (6). Even during assisted ventilation, measuring driving pressure might be important to identify the patients at risk of self-inflicted lung injury (7-9), but the measurement of P_{plat} is still questioned since it requires inspiratory and expiratory muscle relaxation during the occlusion maneuver (10). However, it has been reported that reliable measures of driving pressure can be obtained during PSV (2).

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Our findings demonstrate that measurement of P_{plat} and assessment of respiratory mechanics is feasible also during NAVA, an innovative mode of assisted mechanical ventilation. We observed a good correlation between values of CPL_{RS} obtained during NAVA and PSV. Increasing the NAVA level was associated with an increase in P_{vent}, but driving pressure was unaffected since Vt did not change and the pressure developed by the inspiratory muscles decreased. In our population, we also observed that increasing PEEP from 6 to 12 cmH_2O was associated with a reduction of driving pressure and an improvement in CPL_{RS}.

Our study has limitations. First, all measures were obtained without checking for intrinsic PEEP, which is difficult to estimate during spontaneous breathing. Second, values of CPL_{RS} obtained during PSV (and not during controlled ventilation) were considered as “reference” for the measures obtained during NAVA. However, assessment of respiratory mechanics during PSV has been suggested by several Authors, and we believe that the good correlation we observed between two different assisted ventilation modes confirms the feasibility of P_{plat} measurement not only during controlled ventilation.

In conclusion, P_{plat} measurement by means of an end-inspiratory occlusion maneuver is feasible during NAVA, and allows assessment of respiratory mechanics and estimation of the balance between ventilator assistance and patient effort.

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Table

Table 1. Effects of varying Neurally Adjusted Ventilatory Assist (NAVA) and positive end-expiratory pressure (PEEP) levels on respiratory parameters during end-inspiratory occlusion maneuvers.

	% of baseline NAVA level				PEEP level (cmH_2O)		
	50	100	150	p value	PEEP 6	PEEP 12	p value
Tidal volume (ml/kg pbw)	7.2 (5.4-8.3)	7.3 (5.6-9.2)	6.9 (5.6-8.3)	0.08	7.0 (5.6-9.0)	7.1 (5.3-8.2)	0.21
Peak of EAdi (μVolt)	6.1 (4.1-12.1)	5.6 (3.5-9.7)	4.6 (2.9-7.0)	0.21	5.5 (3.9-10.9)	5.3 (3.2-9.2)	**< 0.05**
Plateau pressure (cmH_2O)	20.8 (17.9-22.8)	22.0 (17.0-25)	21.2 (16.3-24.5)	0.33	17.2(15.5-21.3)	22.6(21.2-25.0)	**< 0.001**
Driving pressure (cmH_2O)	10.4(8.9-13.8)	11.3(9.6-15.6)	10.5(9.6-13.0)	0.33	11.2(9.5-15.3)	10.6(9.2-13.0)	**< 0.01**
Pressure applied by the ventilator (cmH_2O)	12.7(9.2-13.9)	13.8 (11.6-17.4)*	14.9 (12.0-19.2)*	**< 0.001**	10.8 (8.2-12.8)	15.5(13.6-19.0)	**< 0.001**
Pmusc index (cmH_2O)	8.5(6.7-11.0)	7.3(5.5-11.0)	6.7 (3.6-8.0) *, †	**< 0.001**	7.7 (4.6-11.0)	7.2 (5.5-9.4)	**< 0.05**
Compliance of respiratory system (ml/cmH_2O)	42.9(35.9-54.8)	43.7(36.3-51.9)	44.5(36.3-51.7)	0.80	43.0(35.2-49.9)	44.5(36.8-52.6)	**< 0.05**

Definition of abbreviations: Pdw = predicted body weight.

Driving pressure is calculated as plateau pressure minus positive end-expiratory pressure. Pressure applied by the ventilator is defined as peak of EAdi multiplied by NAVA level. Pmusc index is computed as plateau pressure minus pressure applied by the ventilator. Compliance of respiratory system is the ratio between tidal volume and driving pressure. A linear mixed model was applied, considering PEEP and NAVA levels as fixed effects, and subjects as random effect. No interaction was recorded between PEEP and NAVA levels for each considered variable. Data in bold are statistically significant. *) $p < 0.05$ Vs. 50% of baseline NAVA level, †) $p < 0.05$ Vs. baseline NAVA level.

Figure Legends

Figure 1. End-inspiratory occlusion maneuvers during Pressure Support ventilation (PSV) and Neurally Adjusted Ventilatory Assist (NAVA).

Definition of abbreviations: PEEP = positive end-expiratory pressure; Paw = airway pressure; P_{plat} = airway plateau pressure; P_{vent} = pressure applied by the ventilator; PMI = Pmus index; Pes = esophageal pressure; EAdi = electrical activity of diaphragm.

Both end-inspiratory pauses were retrieved in the same patient. PEEP was 6 cmH_2O, while PSV and NAVA levels were 8 cmH_2O and 1 cmH_2O/µVolt, respectively. P_{vent} is PEEP plus PS level during PSV and PEEP plus peak of EAdi multiplied by gain during NAVA. In both modes the driving pressure results from P_{plat} minus PEEP and PMI is computed as P_{plat} minus P_{vent}. Pes and EAdi traces confirm the absence of inspiratory breathing activity during the end-inspiratory occlusions. During the occlusion, Pes turned to positive values reaching a stable plateau. The plateau values of both Paw and Pes reflect the elastic recoil of the respiratory system and chest wall, respectively. In the example shown, EAdi is decreasing at the time of zero-flow (indicating that the patient is starting to relax the diaphragm just before the occlusion), while Pes and Paw reach a plateau as EAdi returns to the baseline value. Hence, expiratory muscles contraction can very unlikely explain the increase in Pes and Paw in a phase of the respiratory cycle immediately after the end of inspiration. However,

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assessment of P_{plat} may be difficult in patients with extremely high respiratory rate or in subjects with active expiration (e.g., obstructive patients).

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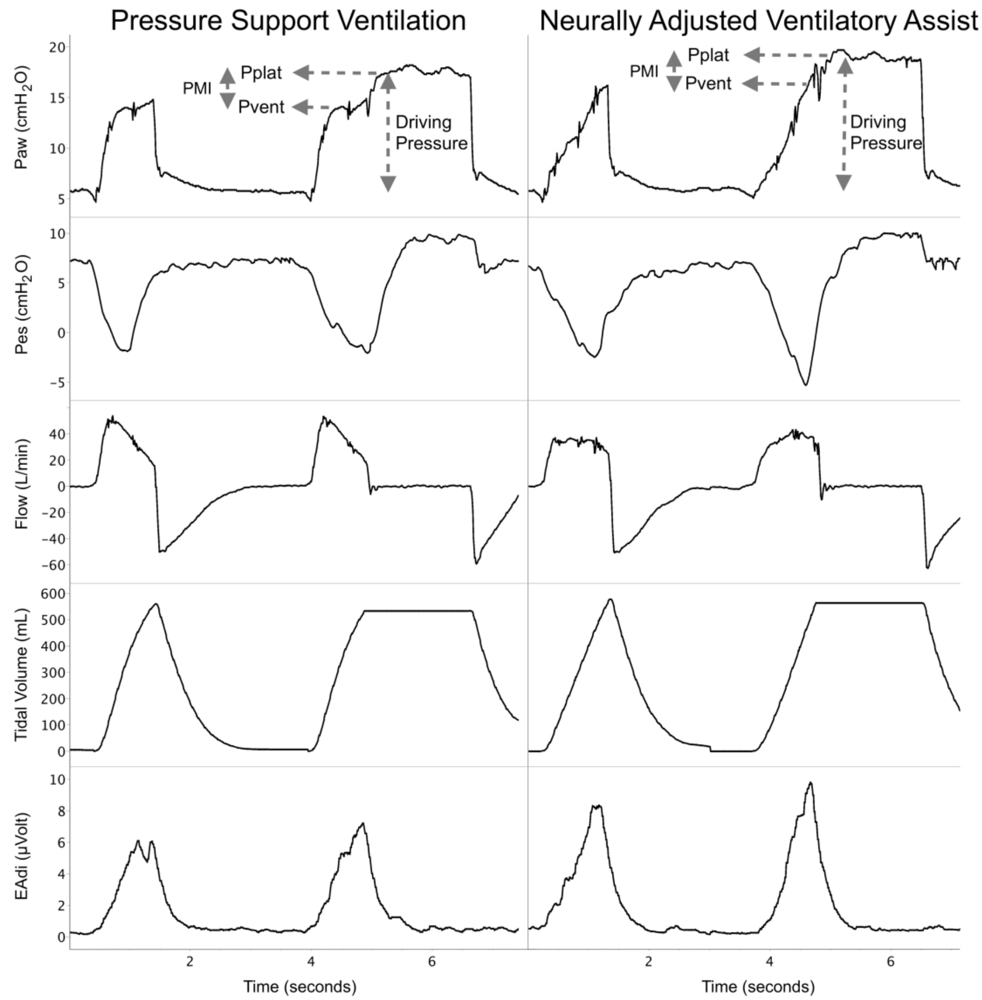

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