



# Neurally adjusted ventilatory assist preserves cerebral blood flow velocity in patients recovering from acute brain injury

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## Abstract

Neurally adjusted ventilatory assist (NAVA) has never been applied in patients recovering from acute brain injury (ABI) because neural respiratory drive could be affected by intracranial disease with detrimental effects on cerebral blood flow (CBF) velocity. Our primary aim was to assess the impact of NAVA and pressure support ventilation (PSV) on CBF velocity. In fifteen adult patients recovering from ABI and undergoing invasive assisted ventilation, PSV and NAVA were applied over 30-min-lasting trials, in the following sequence: PSV<sub>1</sub>, NAVA, and PSV<sub>2</sub>. While PSV was set to deliver a tidal volume ranging between 6 and 8 ml kg<sup>-1</sup> of predicted body weight, in NAVA the level of assistance was chosen to achieve the same inspiratory peak airway pressure as PSV. At the end of each trial, a sonographic evaluation of CBF mean velocity was bilaterally obtained on the middle cerebral artery and an arterial blood gas sample was taken for analysis. CBF mean velocity was 51.8 [41.9,75.2] cm s<sup>-1</sup> at baseline, 51.9 [43.4,71.0] cm s<sup>-1</sup> in PSV<sub>1</sub>, 53.6 [40.7,67.7] cm s<sup>-1</sup> in NAVA, and 49.5 [42.1,70.8] cm s<sup>-1</sup> in PSV<sub>2</sub> ( $p=0.0514$ ) on the left and 50.2 [38.0,77.7] cm s<sup>-1</sup> at baseline, 47.8 [41.7,68.2] cm s<sup>-1</sup> in PSV<sub>1</sub>, 53.9 [40.1,78.5] cm s<sup>-1</sup> in NAVA, and 55.6 [35.9,74.1] cm s<sup>-1</sup> in PSV<sub>2</sub> ( $p=0.8240$ ) on the right side. No differences were detected for pH ( $p=0.0551$ ), arterial carbon dioxide tension ( $p=0.8142$ ), and oxygenation ( $p=0.0928$ ) over the entire study duration. NAVA and PSV preserved CBF velocity in patients recovering from ABI.

**Trial registration:** The present trial was prospectively registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT03721354) on October 18th, 2018.

**Keywords** Acute brain injury · Mechanical ventilation · Cerebral blood flow · Asynchronies

## 1 Introduction

Invasive mechanical ventilation (IMV) is a life-saving intervention in patients admitted to intensive care unit (ICU) with diagnosis of severe acute brain injury [1]. However, IMV management is particularly challenging in this population since deep sedation and a tight control of the arterial carbon dioxide and oxygen tension as well as the intrathoracic pressure are recommended to avoid unsuitable cerebral blood flow changes, particularly at an early stage [2–4]. Thereafter, pressure support ventilation (PSV) is the most widespread ventilatory mode used to lead the patients towards the withdrawal of IMV [5]. However, during PSV, the mismatch between patient demand and mechanical assistance has been frequently reported in terms of asynchrony events, with negative consequences

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on patient-ventilator interaction (PVI) [6, 7]. A poor PVI is associated with worse prognosis due to increased need for sedatives [8], prolongation of mechanical ventilation [6, 9], higher rate of tracheostomy [6], longer ICU and hospital stay [10], and increased mortality [11]. Accordingly, the loss of PVI could represent one reason of delayed withdrawal from IMV and/or extubation failure in neurocritical care patients too.

Neurally adjusted ventilatory assist (NAVA) is a ventilation mode in which the patient can assume the full control of ventilatory assistance in terms of timing and magnitude [12]. In general ICU patients, NAVA improves PVI during invasive and non-invasive ventilation respect to PSV [13–18]. This depends on several aspects: (1) contrarily to PSV where a pneumatic trigger is adopted, during NAVA the ventilator is triggered by patient's electrical activity of diaphragm (Eadi); (2) the ventilatory assistance is proportional to Eadi in NAVA, whereas in PSV the ventilatory support is fixed [12]. Thus, NAVA enhances the patient-ventilator synchrony, reduces the incidence of asynchronies, and improves the breath-by-breath variability of tidal volume ( $V_T$ ) compared to PSV [12], mimicking a more physiological behaviour [19]. Up to now, NAVA has never been applied to neurocritical care patients probably due to safety concerns on how the intracranial disease could affect Eadi signal, leading to unwanted modifications of arterial blood gases (ABGs) and cerebral blood flow velocity.

The present physiologic cross-over study was designed to investigate if NAVA could be safely employed in patients recovering from acute brain injury. Accordingly, the primary aim of our investigation was to ascertain and compare the effects of NAVA and PSV on mean cerebral blood flow velocity ( $FV_{\text{mean}}$ ), bilaterally acquired through B-mode trans-cranial color-coded duplex (TCCD) sonography of middle cerebral artery (MCA), in patients recovering from acute brain injury. As additional endpoints the effects of the two ventilatory modes on ABGs as well as cerebral and systemic haemodynamics were investigated. Secondly, the effects on PVI were assessed and compared between two ventilatory modes.

## 2 Methods

Our study was conducted according to the Helsinki Declaration principles, approved by the local Ethical Committee of Azienda Ospedaliero-Universitaria “Maggiore della Carità”- Novara, Italy (protocol No. CE 114/18) and registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT03721354). Written informed consent was obtained for all subjects according to local regulations.

### 2.1 Patients

All adult patients, recovering from acute brain injury and undergoing IMV in PSV mode and continuous intracranial pressure (ICP) monitoring, were enrolled. Exclusion criteria were the following: ICP > 15 mmHg with a 30°-head-up position, documented vasospasm or mean cerebral blood flow velocity bilaterally assessed at middle cerebral artery  $\geq 120 \text{ cm s}^{-1}$  [20], hemodynamic instability despite adequate filling (i.e. need for continuous infusion of epinephrine or vasopressin, or dopamine >  $5 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$  or norepinephrine >  $0.1 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$  to maintain systolic arterial blood pressure > 90 mmHg) [14], core temperature > 38 °C, contraindication to gastro-esophageal catheter positioning [14], and pregnancy.

### 2.2 Study protocol

After the patients met the inclusion criteria, a dedicated feeding tube (Edi Catheter, Getinge, Sweden) was inserted and connected to the ventilator for the Eadi signal acquisition. The correct catheter position was assured as previously described [14].

The patients underwent three 30-min-lasting trials in the following sequence: PSV<sub>1</sub>, NAVA, and PSV<sub>2</sub>. In PSV<sub>1</sub>, inspiratory pressure support over positive end-expiratory pressure (PEEP) was titrated to obtain a  $V_T$  of 6–8 ml<sup>-1</sup> kg<sup>-1</sup> of predicted body weight. The flow trigger was set as more sensible as possible, avoiding auto-triggers, and the expiratory cycle-off threshold was 30% of the peak inspiratory flow. Then, the corresponding level of assistance in NAVA was chosen through a specific ventilator tool (NAVA-preview, Getinge, Sweden) that, during PSV, matches the NAVA gain to get an equivalent peak of inspiratory pressure [14]. Afterwards, the ventilator was switched to PSV, and PSV<sub>1</sub> setting parameters were restored (PSV<sub>2</sub>). PEEP and inspired oxygen fraction were maintained constant at the pre-enrolment values over the whole study duration. The level of sedation was assessed through Richmond Agitation Sedation Scale at study entry, immediately after the definitive catheter positioning, and held stable at each study step. The last minute of each trial was recorded, stored on a personal computer, and furtherly analysed.

### 2.3 Measurements and data analysis

At the end of each trial, an arterial blood sample was taken to obtain the blood gas analysis. Simultaneously, across the temporal window,  $FV_{\text{mean}}$  and pulsatility index (PI) of MCA were blindly assessed through a 2-MHz-TCCD machine (Xario 200, Toshiba Medical System, Japan) on each side, being MCA

flow a rough representation of the ipsilateral hemisphere blood flow [21, 22]. During each assessment, after the MAC identification, the probe position was adjusted, by assuring an insonation angle  $< 30^\circ$  [23], to scan the blood flow velocity at 3 different sampling distances, approximatively: 60 mm, 45 mm, and 35 mm [22]. From the vessel segment showing the highest blood velocity,  $FV_{\text{mean}}$  and PI were computed as the time-mean value of the velocity spectrum outline from 10 consecutive cardiac cycles [24]. ICP, cranial perfusion pressure (CPP), mean arterial pressure, and heart rate were monitored throughout the whole study duration and their average values were collected during the last minute of each trial and finally analysed.

Airflow, airway pressure (Paw) and Eadi were recorded from the ventilator by a dedicated software (Nava Tracker, Getinge, Sweden) through a RS232 interface, at a 100-Hz-sampling rate, stored on a personal computer, and analysed using a specific software (ICU-Lab, KleisTek, Bari, Italy). Paw and Eadi peak were measured. From flow trace mechanical respiratory rate, inspiratory and expiratory time, total breath duration, inspiratory duty cycle, and  $V_T$ , by digital integration, were obtained [14]. Neural respiratory rate, inspiratory and expiratory time, total breath duration, inspiratory duty cycle were attained from Eadi waveform [14]. Inspiratory and expiratory trigger delay as well as time of synchrony, also indexed on neural inspiratory time and expressed in percentage, were calculated [13, 17]. The asynchrony index was computed as total amount of macroasynchrony events (ineffective efforts, double triggers, autotrigger and reverse triggers) on the sum of triggered and non-triggered breaths ratio and expressed in percentage [25]. An asynchrony index  $\geq 10\%$  was deemed suggestive for high rate of macroasynchrony [6]. Finally, the coefficient of variation for  $V_T$ , mechanical respiratory rate, and Eadi and Paw peak were calculated (standard deviation to mean ratio multiplied by 100) as previously described [14].

The sample size of the present study was chosen in keeping with a previous investigation ascertaining the physiologic response to NAVA application in intubated acute respiratory failure patients [14]. Data are presented as median and [25th, 75th percentile]. According to the non-normal distribution of the data, Friedman's test with Dunn's multiple comparisons post-hoc test for repeated measure were employed. The number of patients with Asynchrony index  $\geq 10\%$  was compared among PSV<sub>1</sub>, NAVA, and PSV<sub>2</sub> using Chi-square test. Data analysis was conducted through a dedicated statistical software (Prism 8, Graphpad, California).

### 3 Results

From November 2018 to August 2019, a total number of 22 patients, recovering from acute brain injury, were screened for eligibility, 15 of whom were enrolled and finally analysed

(Supplemental digital content 1). Patients general characteristics and clinical features at the time of enrolment are reported in Table 1.

As described in Table 2, the  $FV_{\text{mean}}$  and PI, assessed at middle cerebral artery on each side, remained stable over the whole study period, without difference among ventilatory modes. Moreover, ICP and CPP as well as systemic haemodynamics and ABGs did not change switching from PSV<sub>1</sub> to NAVA and from NAVA to PSV<sub>2</sub>. Only lactate was reduced moving from PSV<sub>1</sub> to NAVA ( $p=0.0433$ ) without clinical relevance.

Breathing pattern and PVI are reported in Table 3. Expired  $V_T$ , mechanical and neural respiratory rate and timing were not affected by ventilatory mode running. No differences regarding PEEP and Paw peak were detected between PSV<sub>1</sub>, NAVA, and PSV<sub>2</sub>. Peak of Eadi was reduced moving from NAVA to PSV<sub>2</sub> ( $p=0.0318$ ). Inspiratory trigger delay improved switching from PSV<sub>1</sub> to NAVA ( $p=0.0105$ ), whereas expiratory trigger delay decreased during NAVA compared to that recorded during both PSV<sub>1</sub> ( $p=0.0185$ ) and PSV<sub>2</sub> ( $p=0.0185$ ), respectively. Time of synchrony ameliorated with NAVA application respect to PSV<sub>1</sub> ( $p=0.0185$ ) and, when indexed to neural time, it was greater in NAVA compared to both PSV<sub>1</sub> ( $p=0.0016$ ) and PSV<sub>2</sub> ( $p=0.0381$ ). Unlike NAVA, PSV induced a wide worsening of asynchrony index in both trials (vs PSV<sub>1</sub>  $p=0.0318$ ; vs PSV<sub>2</sub>  $p=0.0243$ ) and, as depicted in Fig. 1, the number of patients who experienced an asynchrony index  $\geq 10\%$  was 11/15 (73.3%) in PSV<sub>1</sub>, 5/15 (30%) in NAVA, and 15/15 (100%) in PSV<sub>2</sub> ( $p=0.0004$ ), respectively.

Figure 2 shows the incidence of macroasynchrony events recorded over the whole study duration. Ineffective efforts and autotrigger mainly occurred during PSV<sub>1</sub> (62.07%; 26.44%) and PSV<sub>2</sub> (67.07%; 30.49%). On the contrary, double triggers were poorly represented, being 11.49% and 2.44% of the total amount of asynchrony events in PSV<sub>1</sub> and PSV<sub>2</sub>, respectively. In NAVA, ineffective efforts, autotrigger, and double triggers accounted for 39.13%, 43.48%, and 17.39% of the total number of macroasynchronies detected, respectively. No reverse triggers were noted during all the trials.

The variability of  $V_T$ , mechanical respiratory rate, Paw and Eadi peak are reported in Table 4. Coefficient of variation of  $V_T$  and peak of Paw were higher in NAVA than in PSV<sub>1</sub> ( $p=0.0004$ ;  $p=0.0030$ ) and PSV<sub>2</sub> ( $p=0.0185$ ;  $p<0.0001$ ), respectively.

### 4 Discussion

The main findings of our study can be summarized as follows: (1) in a very short time frame, NAVA and PSV were safely employed in our neurocritical care patients, as  $FV_{\text{mean}}$ ,

**Table 1** Demographic and clinical characteristics at enrollment

Patients	Gender	Age (years)	PBW (kg)	BMI (kg m <sup>-2</sup> )	Admission diagnosis	GCS	RASS	PEEP (cm H <sub>2</sub> O)	PS (cm H <sub>2</sub> O)	FiO <sub>2</sub>	SAPS II	Days of IMV
1	F	77	56.9	33.1	ICH	9	-4	10	12	0.4	37	4
2	M	67	65.9	24.2	ICH	3	-3	5	10	0.4	20	3
3	F	61	52.4	35.2	ICH	4	-4	12	10	0.5	55	8
4	M	55	65.9	26.0	TBI	5	-3	5	5	0.4	26	7
5	M	64	75.0	20.1	PCFI	7	-3	5	5	0.35	29	5
6	F	61	52.4	29.3	PCFI	6	-3	5	10	0.4	39	12
7	M	46	79.5	26.3	SAH	3	-1	12	8	0.3	22	13
8	M	71	79.5	23.4	SAH	6	-4	10	8	0.5	46	7
9	F	35	61.4	22.5	TBI	8	-4	5	8	0.21	27	5
10	F	74	59.6	31.9	SAH	14	-3	8	8	0.3	34	3
11	M	69	70.5	24.5	ICH	4	-3	7	5	0.4	36	15
12	M	66	65.9	26.0	ICH	9	-2	10	5	0.3	37	11
13	M	70	70.5	26.2	PCFI	3	-3	8	8	0.3	42	5
14	F	80	47.9	27.1	ICH	7	-3	8	5	0.3	43	5
15	M	36	65.9	22.5	ICH	6	-3	7	5	0.25	44	12
Overall	6F/9M	66.0 [58.0, 70.5]	65.9 [58.3, 70.5]	26.0 [23.8, 28.2]		6 [4.0, 7.5]	-3.0 [-3.5, -3.0]	8.0 [5.0, 10.0]	8.0 [5.0, 9.0]	0.35 [0.30, 0.40]	37.0 [28.0, 42.5]	7.0 [5.0, 11.0]

PBW predicted body weight, BMI body mass index, GCS Glasgow Coma Scale score at admission, RASS Richmond Agitation-Sedation Scale, PEEP positive end-expiratory pressure, FiO<sub>2</sub> inspired oxygen fraction, SAPSII Simplified Acute Physiology Score II, IMV invasive mechanical ventilation, M male, F female, ICH intra-cerebral hematoma/hemorrhage, TBI traumatic brain injury, PCFI posterior cerebral fossa ischemia, SAH subarachnoid hemorrhage (aneurysm), the frequency of distribution and the median and [25th, 75th percentile] are reported in the bottom line

**Table 2** Cerebral blood flow velocity, intracranial pressure, hemodynamics, and arterial blood gases

Variables	Study steps				<i>p</i> -value
	Baseline	PSV <sub>1</sub>	NAVA	PSV <sub>2</sub>	
<i>MCA Cerebral blood flow velocity</i>					
Left FV <sub>mean</sub> (cm s <sup>-1</sup> )	51.8 [41.9, 75.2]	51.9 [43.4, 71.0]	53.6 [40.7, 67.7]	49.5 [42.1, 70.8]	0.0514
Right FV <sub>mean</sub> (cm s <sup>-1</sup> )	50.2 [38.0, 77.7]	47.8 [41.7, 68.2]	53.9 [40.1, 78.5]	55.6 [35.9, 74.1]	0.8240
Left PI	1.3 [1.1, 1.5]	1.3 [1.2, 1.5]	1.3 [1.2, 1.5]	1.4 [1.2, 1.5]	0.7491
Right PI	1.3 [1.3, 1.4]	1.4 [1.1, 1.5]	1.3 [1.1, 1.5]	1.3 [1.1, 1.5]	0.8710
<i>Intracranial pressure and hemodynamics</i>					
ICP (mm Hg)	5.0 [2.0, 10.0]	4.0 [3.0, 8.0]	6.0 [3.0, 9.0]	5.0 [3.0, 10.0]	0.9189
CPP (mm Hg)	88.0 [66.0, 90.0]	80.0 [72.7, 90.0]	82.0 [76.0, 87.0]	82.0 [72.0, 93.0]	0.6700
<i>Systemic hemodynamics</i>					
MAP (mm Hg)	93.0 [79.0, 98.0]	87.0 [77.0, 93.0]	90.0 [78.7, 95]	89.0 [79.0, 97.0]	0.2959
HR (beats min <sup>-1</sup> )	80.0 [64.0, 88.0]	76.0 [65.0, 92.0]	74.0 [65.0, 90.0]	72.0 [63.0, 97.0]	0.1940
<i>Arterial blood gases</i>					
pH	7.4 [7.4, 7.5]	7.4 [7.4, 7.5]	7.4 [7.4, 7.5]	7.4 [7.4, 7.5]	0.0551
PaCO <sub>2</sub> (mm Hg)	41.9 [39.4, 45.5]	42.2 [38.6, 45.2]	43.4 [39.3, 45.5]	40.9 [39.5, 45.7]	0.8142
PaO <sub>2</sub> /FiO <sub>2</sub> (mm Hg)	222.0 [199.0, 260.0]	235.0 [198.0, 284.0]	264.0 [226.0, 305.0]	278.0 [197.0, 304.0]	0.0928
Lactate (mmol l <sup>-1</sup> )	0.7 [0.5, 1.0]	0.7 [0.5, 1.1]	0.6 [0.4, 0.9]*	0.6 [0.4, 1.0]	0.0044

Data are presented as median and [25th, 75th percentile]. *p*-values derive from non-parametric Friedman's test for repeated measures, whereas symbols refer to *p*-values from multiple comparison post-hoc Dunn's test

PSV<sub>1</sub> pressure support ventilation mode trial 1, NAVA neurally adjusted ventilatory assist ventilation mode, PSV<sub>2</sub> pressure support ventilation mode trial 2, MCA middle cerebral artery, FV<sub>mean</sub> mean cerebral blood flow velocity assessed at MCA through transcranial color duplex sonography technique, PI pulsatility index assessed at MCA through transcranial color doppler technique, ICP intracranial pressure, CPP cerebral perfusion pressure, MAP mean arterial pressure, HR heart rate, PaCO<sub>2</sub> arterial carbon dioxide tension, PaO<sub>2</sub>/FiO<sub>2</sub> arterial oxygen tension on inspired oxygen fraction ratio

\**p* < 0.05 vs. Baseline

PI, ABGs, cerebral and systemic haemodynamics were stable over all study duration; (2) in our series, NAVA, contrarily to PSV, improved PVI by ameliorating patient-ventilator synchrony, reducing the macrosynchronies incidence, and providing a better breath-by-breath V<sub>T</sub> and Paw peak variability.

Cerebral blood flow is the most important determinant of oxygen delivery to brain [26]. In acutely brain-injured patients, the cerebral blood flow and oxygen delivery optimization depends on ICP [27, 28], CPP [27, 28], carbon-dioxide tension [29, 30], and systemic oxygenation [31]. Accordingly, mechanical ventilation should be set to improve systemic oxygenation [31], to maintain an arterial carbon dioxide tension within a 32–45 mmHg range [32], and to prevent excessive rise of intrathoracic pressure that could induce the worsening of CPP [33], especially in the early stages of acute brain injury.

Following the early phases of acute brain injury, PSV is commonly employed as a safe ventilatory strategy during the weaning process from IMV [5, 34]. Here we show that both PSV and NAVA were securely applied in our setting, since FV<sub>mean</sub>, assessed at MCA on each side through TCCD sonography, was equally preserved by both ventilatory modes. This finding could be ascribed to three mechanisms;

(1) the absence of pathological modifications of ICP during the entire study period, as also suggested by the fact that PI did not change over the trials [35]; (2) the lack of clinically relevant variations of cerebral and systemic haemodynamics, in agreement with the fact that CPP and mean arterial pressure did not change switching from PSV to NAVA; (3) the preservation of a physiological arterial carbon dioxide tension and ABGs overall, despite the mode of ventilation running. This aspect was particularly relevant, because it confirmed that the negative feedback loop of chemical control of respiration was preserved in our population. Indeed, we could speculate that the alveolar ventilation was similar among ventilation modes, as suggested by the absence of modifications of V<sub>T</sub>, mechanical respiratory rate, and arterial carbon dioxide tension among trials. In NAVA, this was the result of a higher respiratory centre output, as confirmed by a greater Eadi peak compared to that detected in PSV<sub>1</sub> and PSV<sub>2</sub>, respectively. Thus, being the ventilatory support applied in proportion to Eadi [12], in NAVA, the mechanical ventilation was fully controlled by patient's own respiratory centres.

Despite the level of assistance, NAVA assured a low-tidal protective ventilation, in general acute respiratory failure patients [14]. In line with previous findings, in our

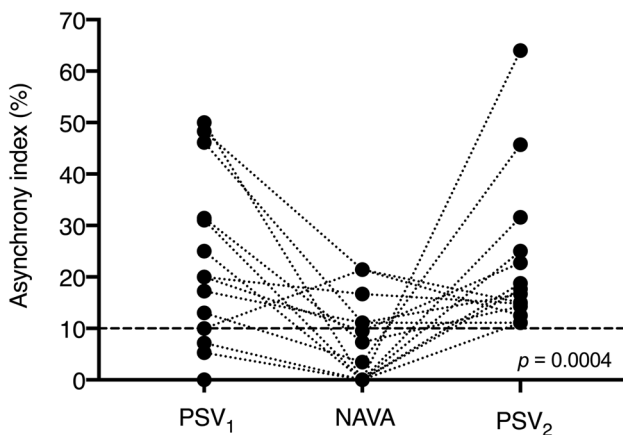
**Table 3** Breathing pattern, and patient-ventilator interaction

Variables	Study steps			
	PSV <sub>1</sub>	NAVA	PSV <sub>2</sub>	<i>p</i> -value
<i>Breathing pattern</i>				
Expired V <sub>T</sub> (ml kg <sup>-1</sup> of PBW)	7.3 [6.4, 7.9]	6.9 [6.5, 8.2]	6.8 [6.2, 7.8]	0.0569
RR <sub>mec</sub> (mechanical breathes min <sup>-1</sup> )	18.4 [15.9, 21.9]	18.1 [15.0, 26.5]	17.3 [15.5, 24.8]	0.4841
RR <sub>neu</sub> (neural breathes min <sup>-1</sup> )	19.0 [15.0, 25.0]	17.0 [14.0, 25.0]	19.0 [16.0, 29.0]	0.2588
TI <sub>mec</sub> (s)	1.0 [0.9, 1.2]	0.9 [0.7, 1.2]	0.9 [0.9, 1.2]	0.0743
TI <sub>neu</sub> (s)	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	1.1 [0.8, 1.2]	0.4204
TE <sub>mec</sub> (s)	2.4 [1.8, 2.7]	2.0 [1.6, 2.8]	2.5 [1.5, 3.1]	0.6271
TE <sub>neu</sub> (s)	1.0 [0.9, 1.1]	1.1 [1.0, 1.2]	1.1 [1.0, 1.2]	0.0381
TI/TTOT <sub>mec</sub>	0.3 [0.3, 0.5]	0.3 [0.3, 0.4]	0.3 [0.3, 0.4]	0.6271
TI/TTOT <sub>neu</sub>	0.5 [0.5, 0.5]	0.5 [0.4, 0.5]	0.5 [0.4, 0.5]	0.2818
<i>Patient-ventilator interaction</i>				
PEEP (cm H <sub>2</sub> O)	7.9 [4.7, 9.9]	7.6 [4.9, 10.0]	7.6 [4.7, 9.8]	0.4080
Paw <sub>peak</sub> (cm H <sub>2</sub> O)	14.4 [11.2, 15.6]	13.3 [10.3, 16.2]	13.0 [11.0, 15.5]	0.6271
Eadi <sub>peak</sub> (μV)	2.1 [1.5, 5.5]	3.4 [2.4, 7.3]	2.5 [1.9, 4.2] <sup>†</sup>	0.0171
Inspiratory Delay <sub>trigger</sub> (s)	0.4 [0.3, 0.6]	0.2 [0.2, 0.3]*	0.4 [0.4, 0.5]	0.0115
Expiratory Delay <sub>trigger</sub> (s)	0.3 [0.2, 0.5]	0.2 [0.2, 0.3]*	0.3 [0.3, 0.5] <sup>†</sup>	0.0067
T <sub>synch</sub> (s)	0.7 [0.5, 0.8]	0.8 [0.6, 1.1]*	0.6 [0.4, 0.8]	0.0150
T <sub>synch</sub> /TI <sub>neu</sub> (%)	57.6 [45.6, 70.1]	79.8 [64.5, 84.1]*	58.0 [46.7, 68.8] <sup>†</sup>	0.0016
Asynchrony Index (%)	20 [7.1, 31.4]	3.4 [0.0, 11.1]*	17.7 [14.3, 25] <sup>†</sup>	0.0079

Data are presented as median and [25th, 75th percentile]. *p*-values derive from non-parametric Friedman’s test for repeated measures, whereas symbols refer to *p*-values from multiple comparison post-hoc Dunn’s test

PSV<sub>1</sub> pressure support ventilation mode trial 1, NAVA neurally adjusted ventilatory assist ventilation mode, PSV<sub>2</sub> pressure support ventilation mode trial 2, V<sub>T</sub> expired tidal volume on predicted body weight ratio, RR<sub>mec</sub> mechanical respiratory rate, RR<sub>neu</sub> neural respiratory rate, TI<sub>mec</sub> mechanical inspiratory time, TI<sub>neu</sub> neural inspiratory time, TE<sub>mec</sub> mechanical expiratory time, TE<sub>neu</sub> neural expiratory time, TI/TTOT<sub>mec</sub> mechanical inspiratory duty cycle, TI/TTOT<sub>neu</sub> neural inspiratory duty cycle, PEEP positive end-expiratory pressure, Paw<sub>peak</sub> peak of airway inspiratory pressure, Eadi<sub>peak</sub> peak of electrical activity of diaphragm, Inspiratory Delay<sub>trigger</sub> inspiratory trigger delay, Expiratory Delay<sub>trigger</sub> expiratory trigger delay, T<sub>synch</sub> Time of synchrony between neural effort and ventilatory support, T<sub>synch</sub>/TI<sub>neu</sub> (%) ratio expressed in percentage, between time during which respiratory effort and ventilator assistance are synchronous on TI<sub>neu</sub>

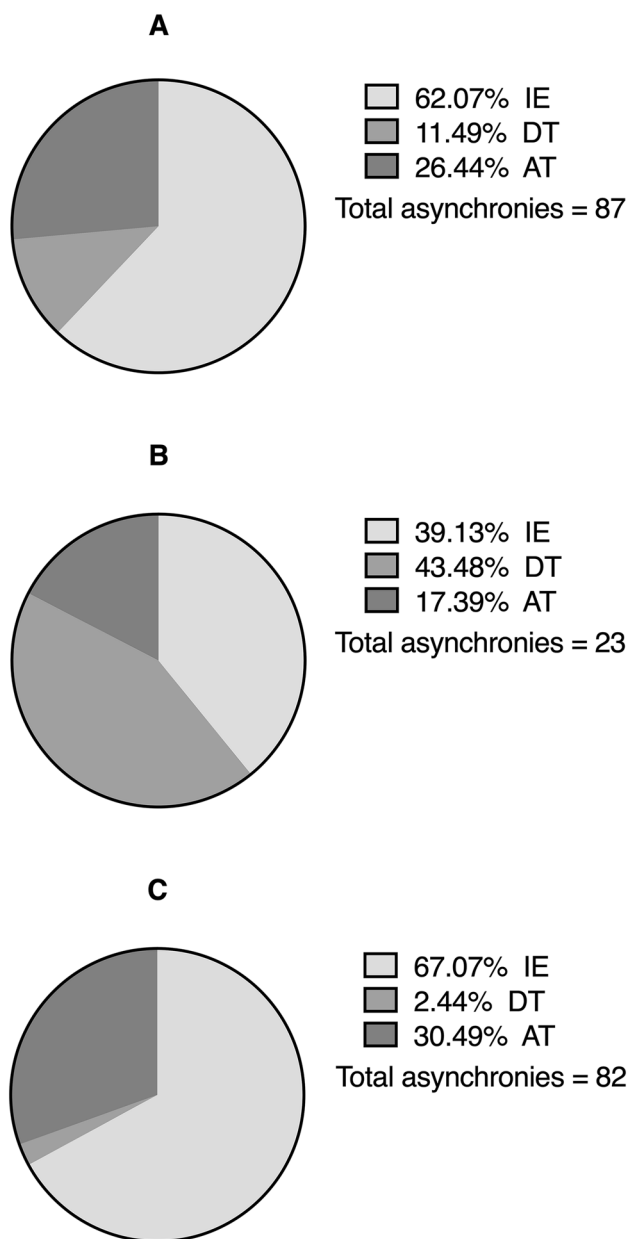
\**p* < 0.05 vs PSV<sub>1</sub>; <sup>†</sup>*p* < 0.05 vs. NAVA



**Fig. 1** Asynchrony index. The asynchrony index of each patient during all study trials are depicted. PSV<sub>1</sub> pressure support ventilation trial 1, NAVA neurally adjusted ventilatory assist ventilation, PSV<sub>2</sub> pressure support ventilation trial 2; *p*-value is referred to Chi-square test among PSV<sub>1</sub>, NAVA, and PSV<sub>2</sub> for asynchrony index ≥ 10%

series, a protective ventilation strategy was adopted and maintained both through PSV and NAVA, being V<sub>T</sub> persistently < 8 ml<sup>-1</sup> kg<sup>-1</sup> of predicted body weight during whole study duration. This could be particularly interesting in patients recovering from acute brain injury with a coexisting acute lung injury. In fact, it has been demonstrated that the neurocritical care patients undergoing high-tidal mechanical ventilation are more prone to ventilator-induced-lung-injury occurrence [36]. In keeping with our results, NAVA could represent a good solution to assure a low-tidal-protective ventilation and prevent ventilator-induced-lung injury after the early phases of acute brain injury.

NAVA, compared to PSV, improves PVI in adult patients, admitted in ICU and undergoing invasive and non-invasive mechanical ventilation, through several mechanisms [13–15, 17, 18, 37, 38]. First of all, NAVA ameliorates the patient-ventilator synchrony by reducing the inspiratory and expiratory trigger delay [13, 15] and increasing the time of



**Fig. 2** Macroasynchrony events. The total number of macroasynchrony events and the percentages of the specific types of asynchronies are depicted. Light grey, *IE* ineffective efforts; middle grey, *DT* double triggers; dark grey, *AT* auto-triggers. **a** Pressure support ventilation trial 1; **b** neurally adjusted ventilatory assist; **c** pressure support ventilation trial 2

synchrony between patient's own neural inspiratory effort and ventilatory assistance, as previously reported also during non-invasive ventilation [17, 18]. In good agreement with previous investigations [13–15, 17, 18, 37, 38], also in our study patient-ventilator matching was better during NAVA application compared to that observed in PSV. Indeed, the inspiratory and expiratory trigger delay in NAVA were shorter than those recorded in PSV. In addition, in our

patients, the time of synchrony, on average, accounted for 74.3% of neural inspiratory time in NAVA and 56.8% and 55.3% in PSV<sub>1</sub> and PSV<sub>2</sub>, respectively.

Generally, during NAVA, the asynchrony index and the incidence of macroasynchrony events are reduced respect to PSV in invasively and non-invasively ventilated patients [14–18]. In good agreement with previous investigations [14–18], also in our setting NAVA improved PVI by diminishing asynchrony index and macroasynchronies occurrence compared to PSV<sub>1</sub> and PSV<sub>2</sub>, respectively. Indeed, only 30% of patients experienced an asynchrony index  $\geq 10\%$  in NAVA against 73.3% and 100% in PSV<sub>1</sub> and PSV<sub>2</sub>, respectively. Thus, the total amount of macroasynchronies was lower in NAVA compared to both PSV trials. Taking into account the different types of asynchronies detected, in PSV<sub>1</sub> and PSV<sub>2</sub> the ineffective efforts were the most detected asynchrony events (among 62% and 67%), followed by autotrigger (among 26% and 30%) and double triggers (among 11% and 2%). Contrariwise, in NAVA, the double triggers (43%) occurred more frequently compared to the ineffective efforts (39%) and autotrigger (17%). No reverse triggers were observed during all the trials. These findings are in line with previous results achieved in intubated patients with acute respiratory failure [15, 16], also undergoing weaning trial [39]. What is novel in our results is that, regardless of ventilatory mode, the asynchrony index and the macroasynchrony events incidence were higher in our patients compared to those reported in previous investigations [14–16, 39]. This could depend on two aspects: (1) neurocritical patients are more prone to asynchronies development probably because of different respiratory drive characteristics [40] compared to those described in acute respiratory failure [14–16]; (2) in handling with acute brain injury, deep sedation levels are more frequently achieved and longer maintained [4] compared to the sedation plans adopted in intubated general ICU patients, with the well-described effects on neural respiratory drive and breathing pattern [41, 42], safety, and outcomes [43, 44].

NAVA enhances PVI preserving the breath-by-breath variability of  $V_T$  mimicking the physiological behaviour of healthy individuals [14, 19]. As matter of fact, while the ventilatory assistance delivered in NAVA is proportional to Eadi [12], during PSV, the patients receive a fixed ventilatory support that, in some cases, leads to lose the control of their own breathing pattern [45]. In keeping with previous works, also in our study,  $V_T$  and  $Paw$  peak variability were better preserved in NAVA compared to those reported in PSV<sub>1</sub> and PSV<sub>2</sub>. On the contrary, the variability of mechanical respiratory rate and Eadi peak were similar among ventilatory modes. Thus, in our neurocritical care patients, a more variable breathing pattern was assured in NAVA, compared to PSV<sub>1</sub> and PSV<sub>2</sub>. Noteworthy, two patients developed in NAVA a Cheyne-Stokes respiration that was barely

**Table 4** Variability of breathing pattern

Variables	Study steps			p-value
	PSV <sub>1</sub>	NAVA	PSV <sub>2</sub>	
<i>Breathing pattern</i>				
V <sub>T</sub> – CV (%)	5.1 [2.8, 12.5]	19.8 [9.5, 26.7]*	9.1 [4.9, 15.5] <sup>†</sup>	0.0004
RR <sub>mec</sub> – CV (%)	7.0 [4.7, 12.0]	8.2 [5.4, 28.6]	10.3 [6.0, 17.7]	0.6271
Paw <sub>peak</sub> – CV (%)	2.8 [1.1, 3.3]	14.8 [8.3, 17.5]*	2.2 [1.2, 4.7] <sup>†</sup>	< 0.0001
Eadi <sub>peak</sub> – CV (%)	29.4 [16.8, 40.1]	26.5 [19.3, 34.1]	28.0 [19.4, 34.2]	0.6271

Data are presented as median and [25th, 75th percentile]. *p*-values derive from non-parametric Friedman's test for repeated measures, whereas symbols refer to *p*-values from multiple comparison post-hoc Dunn's test

PSV<sub>1</sub> pressure support ventilation mode trial 1, NAVA neurally adjusted ventilatory assist ventilation mode, PSV<sub>2</sub> pressure support ventilation mode trial 2, V<sub>T</sub> – CV coefficient of variation of expired tidal volume, RR<sub>mec</sub> – CV coefficient of variation of mechanical respiratory rate, Paw<sub>peak</sub> – CV, coefficient of variation of airway inspiratory peak pressure, Eadi<sub>peak</sub> – CV coefficient of variation of diaphragmatic electrical activity peak

\**p* < 0.05 vs. PSV<sub>1</sub>, <sup>†</sup>*p* < 0.05 vs. NAVA

detectable in PSV in absence of pathological modification of FV<sub>mean</sub>, ICP, cerebral haemodynamics and ABGs [46].

Our study has several limitations that deserve discussion. First, our results have been achieved across three 30-min-lasting trials of ventilatory mode application. Although this observation time might seem quite short, it is in agreement with previous investigations evaluating not only NAVA application in invasive and non-invasive setting in course of acute respiratory failure [14, 17] but also the effects of arterial carbon dioxide tension modifications on cerebral blood flow velocity in anesthetized patients having surgery [47]. Second, the considered patients sample size was quite small. Nevertheless, it was in line with the sample sizes reported in several physiologic investigations conducted on NAVA application in different clinical settings [13, 14, 17, 18, 41, 48]. Third, our study population was not homogeneous, mainly in regard to the type of acute brain injury. Further investigations about NAVA application in neurocritical care patients should therefore be planned by focusing on the specific aetiology of acute brain injury. Fourth, aiming to evaluate cerebral blood flow, we bilaterally performed TCCD sonography assessment only at MCA. While a full flow evaluation on three windows (temporal, orbital and foramen magnum) would be the optimal solution, MCA carries 50–60% of the ipsilateral carotid artery blood flow and thus can be considered to represent a great portion of the total blood flow to the hemisphere [21, 22], without losing the validity of our results. Fifth, it is worth to consider the technique limitations of TCCD sonography: (1) being an ultrasound evaluation, it is highly operator-dependent; (2) the measurements are limited to the large basal arteries and can only provide an index of global rather than local cerebral blood flow velocity [23]. To limit these variations, a unique operator conducted the cerebral blood flow sonographic evaluation. Lastly, in our setting a combination of

propofol and remifentanyl in continuous intravenous infusion was adopted as a sedation plan. Accordingly, the effects of these sedatives on neural respiratory drive [41, 42] must be taken into account in interpreting our data.

In conclusion, in our setting, NAVA was safely employed because, as well as PSV, it preserved the cerebral blood flow velocity, gas exchange and haemodynamics. In addition, as expected, NAVA improved PVI by enhancing patient-ventilator synchrony and assuring a more physiological breath-by-breath V<sub>T</sub> variability, compared to PSV. Further studies are needed to investigate the clinical impact of NAVA in specific subsets of acutely-brain-injured patients.

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**Data availability** The data of the present trial will be available on specific request sent to gmcamma@gmail.com.

## Compliance with ethical standards

**Conflict of interest** Dr. Messina reports personal fees and other from Vygon Italia, outside the submitted work. Dr. Navalesi reports personal fees from Getinge, outside the submitted work.

**Ethical approval** The present investigation was approved by Ethical Committee of Azienda Ospedaliero-Universitaria “Maggiore della Carità” - Novara, Italy (protocol No. CE 114/18).

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