NAVA enhances tidal volume and diaphragmatic electro-myographic activity matching: A Range90 analysis of supply and demand

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ABSTRACT

Introduction

Neurally Adjusted Ventilatory Assist (NAVA) is a ventilation assist mode that delivers pressure in proportionality to electrical activity of the diaphragm (*Eadi*). Compared to pressure support ventilation (PS), it improves patient-ventilator synchrony and should allow a better expression of patient's intrinsic respiratory variability. We hypothesize that NAVA provides better matching in ventilator tidal volume (*Vt*) to patients inspiratory demand.

Methods

22 patients with acute respiratory failure, ventilated with PS were included in the study. A comparative study was carried out between PS and NAVA, with NAVA gain ensuring the same peak airway pressure as PS. Robust coefficients of variation (CVR) for *Eadi* and *Vt* were compared for each mode. The integral of *Eadi* (*∫Eadi*) was used to represent patient's inspiratory demand. To evaluate tidal volume and patient's demand matching, Range90 = 5-95% range of the *Vt*/*∫Eadi* ratio was calculated, to normalize and compare differences in demand within and between patients and modes.

Results

In this study, peak *Eadi* and *∫Eadi* are correlated with median correlation of coefficients, R>0.95. Median *∫Eadi, Vt,* neural inspiratory time (Ti_{Neural}), inspiratory time *(Ti)* and peak inspiratory pressure (*PIP*) were similar in PS and NAVA. However, it was found that individual patients have higher or smaller *∫Eadi, Vt,* Ti_{Neural}, *Ti* and PIP. CVR analysis showed greater *Vt* variability for NAVA (p<0.005). Range90 was lower for NAVA than PS for 21 of 22 patients.

Conclusion

NAVA provided better matching of *Vt* to *∫Eadi* for 21 of 22 patients, and provided greater variability *Vt*. These results were achieved regardless of differences in ventilatory demand (*Eadi*) between patients and modes.

Key Words: Mechanical ventilation, NAVA, Variability, Patient-ventilator interaction, Matching.

1.0 INTRODUCTION

In normal subjects, the respiratory centre in the brainstem controls the respiratory pattern namely inspiratory time and expiratory time, inspiratory flow, hence tidal volume (*Vt*). Action potentials generated in the brainstem represent the patients' inspiratory demand. From the brainstem, these action potentials reach the diaphragm, through phrenic nerves then initiating diaphragmatic depolarization and contraction resulting in a flow and pressure variation in the airways which is the beginning of inspiration.

Mechanical ventilation is a widely used therapy in intensive care units (ICUs) for acute respiratory failure [1]. Partial assist ventilation modes that preserve some of the patient's spontaneous respiratory activity are widely used [2,3]. The most used partial assist ventilation mode is the pressure support ventilation (PS) [2,3]. In PS, each ventilator-delivered cycle is initiated by a pneumatic signal (flow or pressure), detected at the upper airway as produced by the patient's inspiratory effort. The pressure delivered is set by the clinician, and the transition of the (assisted) breath into expiration occurs when the inspiratory flow decreases to a predetermined level [4].

Thus, where normal spontaneous breathing patterns show high variability, respiratory variability is reduced under PS. In PS, a constant pressure is delivered by the ventilator regardless of the patient's relative inspiratory effort. As this constant pressure produces the majority of resulting tidal volume (*Vt*) supply, PS is expected to result in reduced *Vt* variability.

Neurally Adjusted Ventilatory Assist (NAVA) is an assisted mode that uses electrical activity of the diaphragm (*Eadi*), an expression of the patient's inspiratory demand, to trigger and cycle off the ventilator, as well as to deliver pressure in direct proportion to *Eadi* [5]. Compared to PS, NAVA improves patient-ventilator interaction by reducing trigger delay, improving expiratory cycling and reducing the number of asynchrony events [6-8]. NAVA also increases respiratory variability in *Vt* and flow related variables compared to PS [6,9]. However, no studies make these comparisons relative to the inspiratory demand (*Eadi*), which may vary between modes and patients. Thus, to determine the true impact of NAVA on *Vt* variability, *Eadi* must be accounted for in the analysis.

It is hypothesized that the magnitude of *Vt* under NAVA would show both better correlation with magnitude of *Eadi* (A better matching between *Vt* with *Eadi*) and greater variability, than with PS. This study aims to confirm these hypotheses by analysis of flow-time and *Eadi*-time curves for PS and NAVA using a simple, new metric (Range90) that quantify the match of *Eadi* demand and *Vt* supply to shows which mode provided a better matching for each patient.

2.0 METHODS

This research analyses prospectively recorded *Eadi*-time and flow-time curves and derived parameters in a study exploring patient-ventilator synchrony on clinically based criteria [7] at the University Hospital of Geneva (Switzerland) and Cliniques Universitaires St-Luc (Brussels, Belgium). The study protocol was approved by the Ethics committee of both participating hospitals.

2.1 Data Recordings

Patients admitted to the ICU, intubated because of acute respiratory failure, and ventilated with PS mode were eligible for the study if they had none of the following exclusion criteria: 1. severe hypoxemia requiring an $FIO_2 \geq 50\%$; 2. hemodynamic instability; 3. known esophageal problem (hiatal hernia, esophageal varicosities); 4. active upper gastro-intestinal bleeding or any other contraindication to the insertion of a naso-gastric tube; 5. age≤16 years old; 6. poor short term prognosis (defined as a high risk of death in the next seven days); or 7. neuromuscular disease. All included patients were ventilated with a Servo-I ventilator (Maquet, Solna, Sweden) equipped with the commercially available NAVA module and software, which delivers both PS and NAVA. The main ventilator settings are reported in Table 1.

Table 1: Main ventilator settings

	PS	NAVA
FIO_2	0.43 ± 0.17	0.43 ± 0.17
PEEP	$7 \pm 2 cmH_2O$	$7 \pm 2 cmH_2O$
Inspiratory Trigger	Flow Trigger: 1.2*l/min* (20/22 patients) Pressure Trigger: -4 to $-5 cmH_2O$ (2/22)	0.5 uV
Expiratory Trigger Sensitivity (ETS)	25-30%	-
PS Level	$13 \pm 3 cmH_2O$	-
Pressurization Slope	100-150*ms*	-
NAVA Gain Level	-	$2.2 \pm 1.8\ cmH_2O/\mu V$

After written informed consent was obtained, the patient's standard nasogastric tube was replaced with NAVA tube. Airway suctioning was performed before the beginning of the protocol. A 20 minute continuous recording (~300-500 breaths) was carried out during standard PS with clinician determined ventilator settings, and then 20 minutes during NAVA with the NAVA level (proportionality factor between recorded *Eadi* and ventilator delivered pressure) set to obtain similar peak airway pressure as the total pressure obtained in PS using previsualization system built in the ventilator. *Eadi* and flow traces were acquired from the Servo-I ventilator and recorded at a frequency of 100Hz by Servo-tracker V4.0 (Maquet, Solna, Sweden). During the entire period, the pressure support level in PS, and NAVA gain in NAVA were kept constant. Equally, positive end expiratory pressure (PEEP), FiO_2, inspiratory trigger, and cycling off settings were maintained constant.

2.2 Data Analysis

Flow-time and *Eadi*-time signal obtained from the Servo-tracker were used to perform the analysis using MATLAB software (The Mathworks, Natick, Massachusetts, USA). A breath was determined by the flow signal, and was defined to commence when the flow signal became positive, and terminate when the flow signal became negative. The flow-time signal was integrated to obtain Vt. $Vt<50ml$ were discarded from analysis. The *Eadi* signal was integrated between the same two time points to obtain the corresponding integrated *Eadi* value ($\int Eadi$), to represent total inspiratory demand [9]. Peak *Eadi* value was captured and compared with $\int Eadi$ to ensure no loss of information. $\int Eadi$ is the time integral of *Eadi* signal and this parameter carries the information on the change of *Eadi* with time, while retaining information on peak *Eadi*. Finally the inspiratory time, Ti (Time when flow becomes positive until time when flow became negative) and neural inspiratory time Ti_{Neural} (Time when flow became positive until time when peak *Eadi* occurs) were calculated as shown in Figure 1.

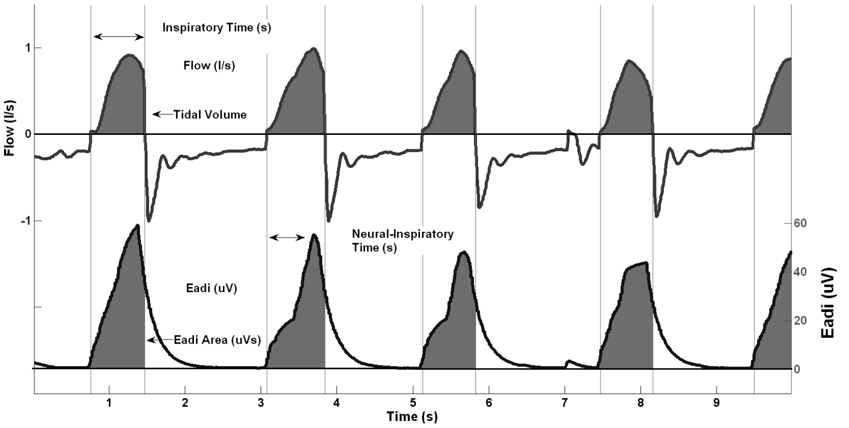

Fig 1 Example of a patient's inspiratory $\int Eadi$ and resulting ventilatory Vt.

2.2.1 Correlation Analysis

Pearson's linear correlation coefficients were calculated for each patient between peak $Eadi$ value and $\int Eadi$, and also between Vt and $\int Eadi$. Two-sample non parametric Kolmogorov-Smirnov goodness-of-fit hypothesis tests were then used to compare PS and NAVA groups.

2.2.2 Variation Analysis – Robust Coefficient of Variation

Traditionally, the Coefficient of Variation (CV = standard deviation/mean) in Vt, $\int Eadi$ and Ti over all breaths for each patient in each ventilator mode was calculated [4,9] for variation analysis. However, normality was assessed using a Kolmogorov-Smirnow test that showed that some parameters were not normally distributed. Hence, the robust coefficient of variation (CVR) was used instead (CVR = median absolute deviation/ median). CVRs for the PS and NAVA group are also compared using a two-sample non parametric Kolmogorov-Smirnov goodness-of-fit hypothesis test.

2.2.3 Matching Analysis – Range90 of Supply over Demand

Vt and $\int Eadi$ were determined and the ratio $Vt/\int Eadi$ was assessed for each breath in both ventilation mode. Vt is the tidal volume given to patients and $\int Eadi$ is defined as an expression for patient's ventilatory demand. The ratio of $Vt/\int Eadi$ is previously defined as Neuroventilatory efficiency, by Passath et al. [10], and this the ratio also carries the information of ventilator supply over patients demand (A form of Patients-ventilator interaction).

For each patient, the empirical cumulative distribution function (CDF) of $Vt/\int Eadi$ ratio in different ventilation modes was plotted. Range90 is calculated as the range 5th to 95th $Vt/\int Eadi$ ratio (Range90 = 95th $Vt/\int Eadi$ – *5th* $Vt/\int Eadi$). A smaller range indicates better matching of the response Vt and, importantly, its variability to the inspiratory $\int Eadi$ demand and its variability. A larger range indicates a lesser ability to match Vt and $\int Eadi$ for each breath regardless of the underlying patient-specific variability in $\int Eadi$. Thus, if Vt variability were equally matched to variability in $\int Eadi$, then the ratio would be more consistent (Range90 will be smaller), and a larger Range90 thus indicates an inability to consistently match Vt to $\int Eadi$ demand. Hence, this ratio normalizes differences in $Eadi$ demand within and between patients and-or ventilatory modes in analysing the resulting Vt variability. The ratio of $Vt/\int Eadi$ for each breath and the analysis of its variability (Range90) over a given mode thus allows fair comparison between modes (for a patient) and between patients, where $Eadi$ demand may vary significantly. The detail description of Range90 and case examples can be found in the electronic supplemental file.

3.0 RESULTS

Twenty-two patients were included in the study. Their major clinical characteristics were the following (mean ± SD): age 66±12 years, BMI 23.4±3.1kg/m^2, recording at 3±2 days post intubation, PaO_2/FIO_2 ratio at inclusion 194.8±58.1$mmHg$. One patient had a history of pulmonary restrictive disease, and 8 patients had a history of pulmonary obstructive disease. For the 22 patients, median [Interquartile (IQR)] $\int Eadi$ were not different between PS and NAVA: 4.10μVs [2.55-5.99] vs 3.97μVs [2.59-6.64]. Ti was 0.97s [0.70-1.15] in PS and 0.80s [0.65-0.92] in NAVA. Median Vt was 468ml [418-514] in PS and 431ml [378-472] in NAVA. Peak inspiratory pressure (PIP) was 21.44cmH_2O [18.57-24.11] in PS and 21.63cmH_2O [19.61-24.56] in NAVA. No significant difference was found between the median these values between PS and NAVA. Table 2 shows the summary of median [IQR] values for $\int Eadi$, Vt, $Ti\_{}_{Neural}$, Ti and peak pressure for all 22 patients for PS and NAVA. The box-whisker plot for $\int Eadi$, Vt, Ti and peak pressure are shown in Figure 2.

Table 2: Summary of $\int Eadi$, Vt, $Ti\_{}_{Neural}$, Ti and peak pressure or 22 patients median [IQR]

	$\int Eadi (\mu Vs)$	Vt (ml)	$Ti\_{}_{Neural}$ (s)	Ti (s)	PIP (cmH_2O)
PS	4.10 [2.55-5.99] [a]	468 [418-514] [a]	0.97 [0.70-1.15] [a]	0.97 [0.70-1.15] [a]	21.44 [18.57-24.11] [a]
NAVA	3.97 [2.59-6.64] [a]	431 [378-472] [a]	0.80 [0.65-0.92] [a]	0.80 [0.65-0.92] [a]	21.63 [19.61-24.56] [a]

[a] p-value >0.005 (See online supplemental file for details)

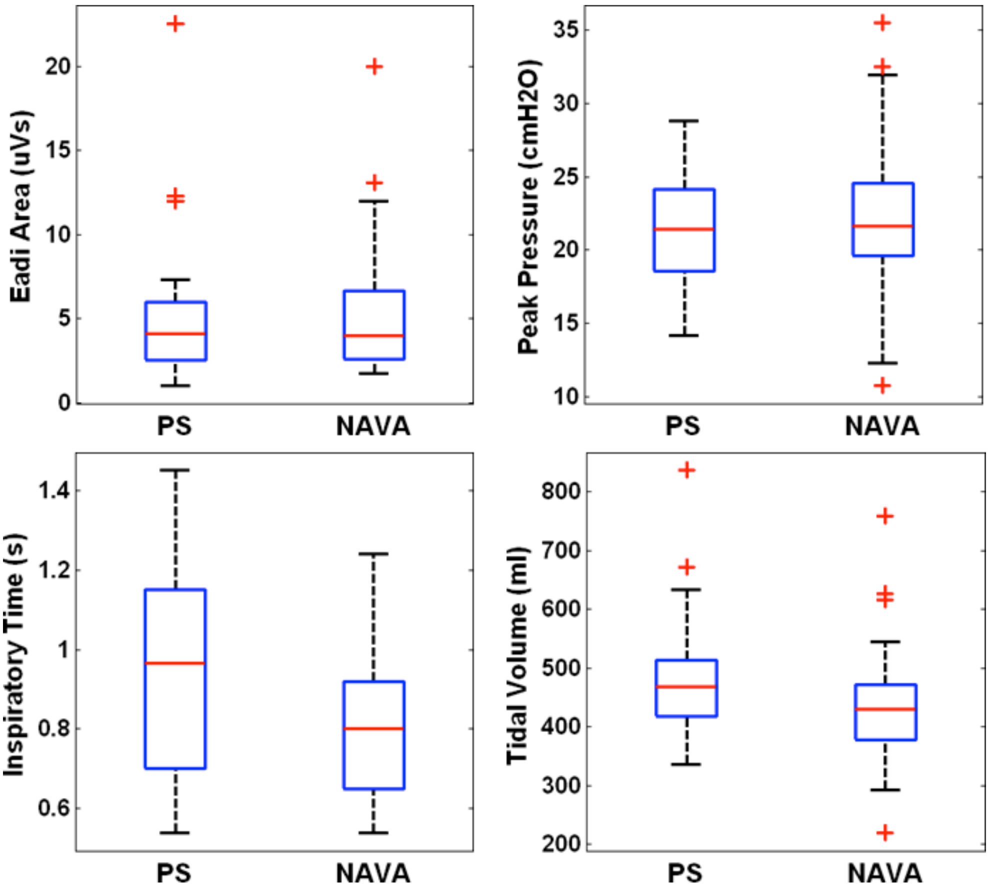

Fig 2 Summary of ∫*Eadi*, *Vt*, *Ti* and *PIP* for all 22 patients in PS and NAVA

3.1 Correlation Analysis

Across all 22 patients, peak *Eadi* and ∫*Eadi* are correlated (median [IQR]) with R = 0.93 [0.88-0.96] for PS and R = 0.87 [0.78-0.90] for NAVA. The correlation of ∫*Eadi* and *Vt* (median [IQR]) for PS is R = 0.50 [0.05-0.65]. For NAVA, R = 0.85 [0.78-0.90]. A two sample Kolmogorov-Smirnov goodness-of-fit hypothesis test shows that the NAVA and PS correlation datasets for ∫*Eadi* and *Vt* are significantly different ($p<0.005$), illustrating the much better correlation seen for NAVA which thus better matches these two variables than PS.

3.2 Variability Analysis

The coefficients of variation (CVR) in *Vt,* ∫*Eadi* and *Ti* are shown in Table 3 for the 22 patients. Using a two-sample Kolmogorov-Smirnov goodness-of-fit hypothesis test, the PS and NAVA CVR in *Vt* are significantly different ($p<0.005$), with the NAVA being more variable. Conversely, no significant difference was observed between ∫*Eadi* or $Ti_{\_Neural}$ CVR, with p = 0.563 and p = 0.332, respectively. More importantly, these results are reported for the population of 22 patients. Individual patients could exhibit a very different variability between PS and NAVA, and the specific variables reported.

Table 3: Robust Coefficient of Variation (CVR) in Vt, $\int Eadi$, $Ti_{\_Neural}$, Ti and PIP (Median [IQR]).

	Median [IQR]	
	PS	**NAVA**
$\int Eadi$	0.211 [0.140-0.326] [b]	0.167 [0.153-0.272] [b]
Vt	0.050 [0.029-0.077] [c]	0.111 [0.076-0.163] [c]
$Ti_{\_Neural}$	0.135 [0.093-0.203] [d]	0.126 [0.094-0.200] [d]
Ti	0.046 [0.031-0.082] [c]	0.093 [0.074-0.138] [c]
PIP	0.006 [0.003-0.008] [c]	0.103 [0.083-0.156] [c]

[b] p-value = 0.563, [c] p-value < 0.005, [d] p-value = 0.979

3.3 Range90 Matching Analysis

For NAVA, the median [IQR; 5th-95th percentile] Range90 = $71.0 ml/\mu Vs$ [36.5-153.6; 15.0-531.3]. For PS, Range90 = $129.9 ml/\mu Vs$ [64.0-341.5; 19.2-645.2]. These results indicate significant variability in the matching of Vt and $\int Eadi$ for both modes, but a consistently lower range for NAVA. The Range90 for both PS and NAVA in all patients are shown in Table 4.

Table 4: PS and NAVA Range90 ($ml/\mu Vs$) for all patients

Patients	PS	NAVA	Range90 Ratio PS/NAVA
1	111.3	76.0	1.47
2	644.4	153.6	4.20
3	330.6	219.0	1.51
4	21.2	17.1	1.24
5	78.2	55.6	1.41
6	64.0	19.9	3.22
7	593.3	515.5	1.16
8	285.2	183.9	1.56
9	42.1	23.2	1.82
10	124.9	103.1	1.22
11	36.0	26.4	1.37
12	62.5	36.5	1.72
13	323.2	50.9	6.35
14	523.1	154.8	3.38
15	125.4	55.8	2.25
16	77.5	44.4	1.75
17	341.5	108.8	3.14
18	134.1	78.4	1.72
19	646.0	76.8	8.42
20	187.8	66.0	2.85
21	375.7	554.9	0.68
22	16.4	11.8	1.39
Median [IQR]	129.8 [64.0-341.5]	71.0 [36.5-153.6]	1.72 [1.39-3.14]

As a larger Range90 value indicates less matching and since the Range90 value is normalized, the value for each mode can be compared. Examining the ratio of Range90 for PS/NAVA, the median [IQR; 5th-95th percentile] of this ratio is 1.72 [1.39-3.14; 0.97-7.18], showing that NAVA consistently had much smaller values than PS. The lower quartile of this Range90 ratio is [0.68-1.39], where only 1 patient had a value less than 1.0, at 0.68. These results show that 21 of 22 patients had better matching of Vt and $\int Eadi$ for NAVA than for PS. 4 patients had values greater than, but near to, 1.0, indicating relatively comparable matching of Vt and $\int Eadi$ between NAVA and PS.

Figure 3 show the CDFs for the ratio of Vt to $\int Eadi$ for 3 specific patients, along with dashed lines indicating the Range90 value. These three patients show a typical case where NAVA better matches Vt and $\int Eadi$ than PS, the one case where PS better matches these variables than NAVA, and one case where they are similar showing the patient with ratio of Range90 values (PS/NAVA = 1.24) that is close to 1.0.

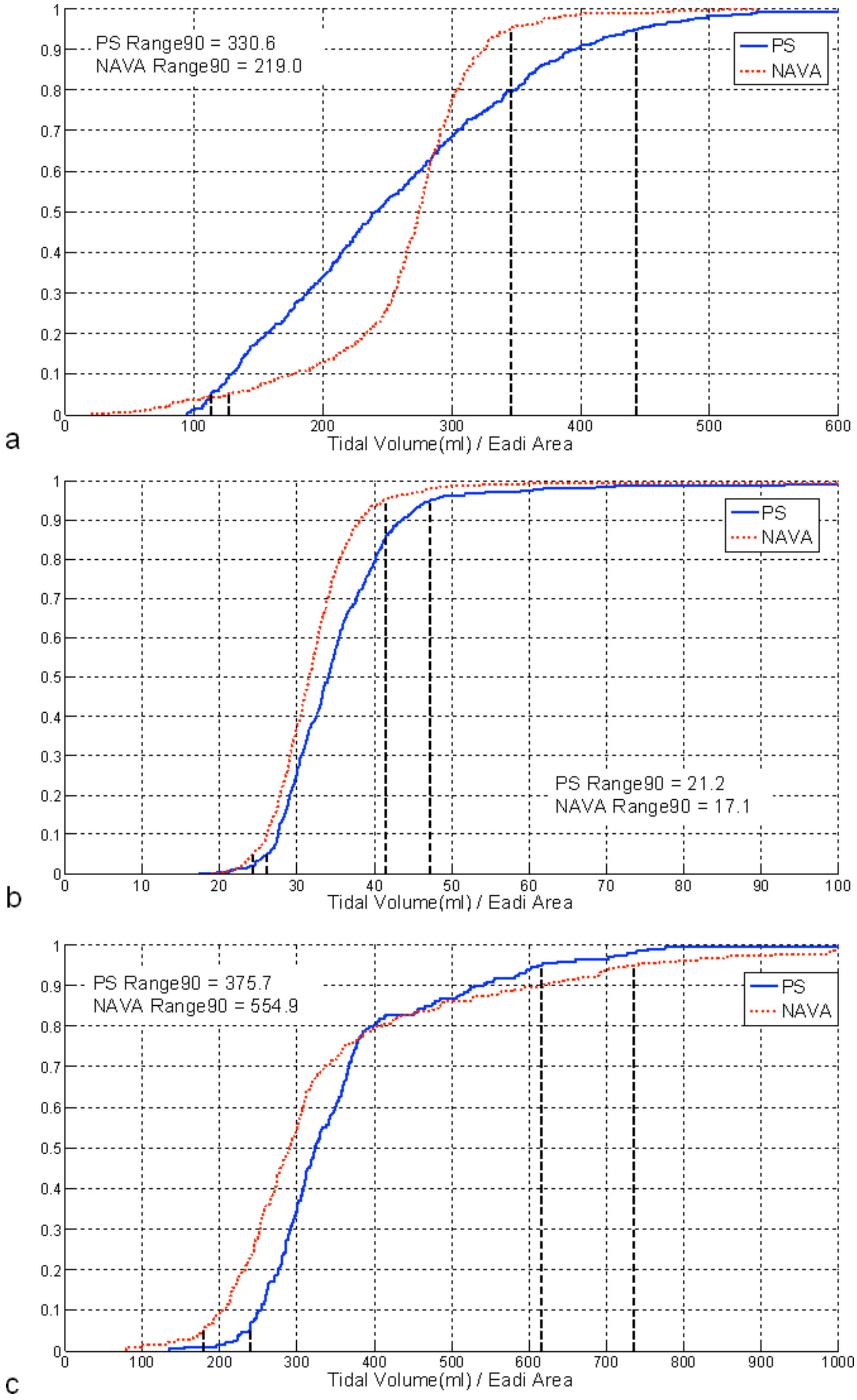

Fig 3 Cumulative distribution function (CDF) plots of *Vt*/∫*Eadi* for both NAVA and PS for three patients. The CDFs show the ~300-400 such values per patient and mode. The dashed lines show the variability (along x-axis) in this ratio or matching, where a narrower band is a smaller Range90 value and thus better matching of *Vt* and ∫*Eadi*. Panels: **a**) Patient 3: NAVA is better than PS; **b**) Patient 4: NAVA and PS are similar; **c**) Patient 21: PS is better than NAVA.

Figure 4 shows two patients, also shown in Figure 3, whose results highlight the differences in ability to match Vt to $\int Eadi$. In particular, the figure plots $\int Eadi$ and Vt for each breath for both modes and each patient. In these figures, it is clear that PS provides a far more constant range of (output) Vt despite similar variation in $\int Eadi$ for both ventilatory modes.

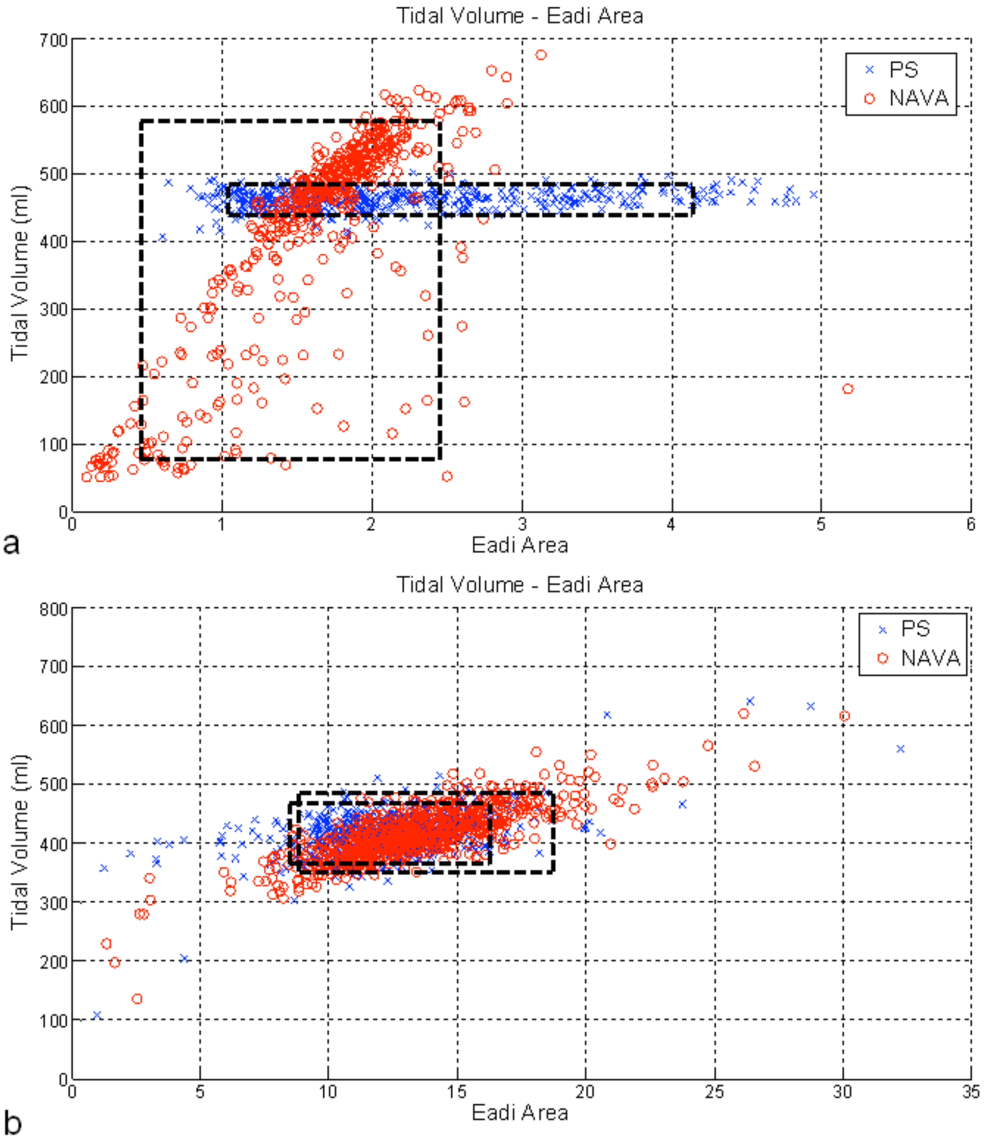

Fig 4 Vt - $\int Eadi$ plots for NAVA and PS. **a)** Patient 3 with PS/NAVA ratio = 1.51. **b)** Patient 4 with PS/NAVA ratio = 1.24. The dashed lines around the data capture the middle 90% of the data for both $\int Eadi$ and Vt for each mode. In both patients, the outcome tidal volume range for the middle 90% of breaths is 50-100mL wide for PS and much wider for NAVA, despite similar input ranges of $\int Eadi$. The smaller ratio of width over height of the box between modes is similar to having a smaller Range90.

4.0 DISCUSSION

Peak *Eadi* and ∫*Eadi* were well correlated under both PS and NAVA ventilation modes. Hence, peak *Eadi* and ∫*Eadi* are essentially identical and could be used to characterize *Eadi* in future studies. ∫*Eadi* is used instead of *Eadi* value in this study as it is more physiologically relevant as total inspiratory demand and readily calculated [9].

Significantly better correlation was observed between *Vt* and ∫*Eadi* under NAVA than PS, indicating that the delivered ventilation is possibly more physiological to the patient under NAVA than PS by better matching the patient's demand and its variability.

Variability in *Vt*, ∫*Eadi* and *Ti* were determined using the traditional method of reporting the robust coefficient of variation (CVR). It was shown that there is no statistically significant difference in the variability of ∫*Eadi*, $Ti_{\_Neural}$ and *PIP* between PS and NAVA over the population of 22 patients. However, the CVRs in *Vt* and *Ti* were significantly different between PS and NAVA ($p<0.005$), with NAVA tidal volumes and inspiratory time more variable. As increased variability has previously been associated with improved ventilation/perfusion ratio and improved oxygenation both in animal models [11-13] and humans [14], the ability of NAVA in maintaining higher variability in tidal volume compared to PS could be of potential clinical interest and will require further investigation. Moreover, overall, it is hypothesized that greater variability in breathing pattern is a healthier patient condition. Thus, it is thought that better patient outcomes could be expected for those patients with a higher variability in ∫*Eadi* when it is equally matched by a high variability in *Vt.* The results presented show that such a result is significantly more likely under NAVA than PS.

In this study, Range90 values were significantly smaller in NAVA then in PS. Of 22 patients, 21 had lower Range90 with NAVA, and only 1 showed a higher ratio with a better match of ∫*Eadi* and *Vt* by PS. Equally, the comparison of Range90 values showed that 4 of the 5 patients comprising the lowest quartile had values near to 1.0 with the 25th percentile value showing the match of *Vt* and ∫*Eadi* was 1.40x better for NAVA than for PS in Range90 value. Hence, ventilation under NAVA is probably more physiological and adapted to the patient's inspiratory demand than under PS.

The importance of normalizing *Vt* variability to its *∫Eadi* variability is highlighted in when it is observed that although there is no significant difference in *∫Eadi* variability over the population in Table 2, *∫Eadi* can be substantially different between PS and NAVA on a patient specific basis. Hence, the patient-specific comparisons of Range90 are particularly relevant, and, equally, account for all breaths directly rather than via a grouped statistic.

The correlation between Range90 with CVR in ∫ Eadi and Vt; For PS, correlation of coefficient R was 0.71 for *∫Eadi*, and 0.67 for *Vt*, compared to NAVA, R = 0.16 for *∫Eadi*, and 0.02 for *Vt*. These results indicated that Range90 is an alternate analysis different from variability analysis, and thus a higher variability does not necessarily mean better 'matching'. The Range90 metric is very simple. Hence, the ventilator *Vt* in response to (not necessarily equally) patient's inspiratory demand can be calculated in real-time. Thus, it could be used to monitor response to ventilator settings and possibly (in future) adapt ventilator settings.

Overall, the results show that PS does not adapt or respond to *∫Eadi* variation, as it provided relatively constant tidal volumes regardless of the magnitude of *∫Eadi*. This point is illustrated in Figure 4. In both cases of Figure 4 the range of tidal volumes seen is very narrow for PS, particularly relative to the *∫Eadi* range. Thus, PS was unable to match *Vt* to the *∫Eadi*.

Prior to this study, Piquilloud et al [7] examined the patient-ventilator asynchronies in pressure support and NAVA, namely ineffective effort, auto-triggering, premature cycling, delayed cycling and double triggering. This work further extends the comparison of PS and NAVA in patients-specific level. In particular, Range90 is a novel method of determining the matching (Synchronisation) of the magnitude of the ventilator supply and magnitude of patient's demand (Neuroventilatory efficiency, *Vt*/*∫Eadi* ratio). The resulting 90% range (Range90) value for each mode shows how well outcome *Vt* was matched by the ventilatory mode to inspiratory demand, *∫Eadi*. A smaller Range90 indicates better matching, thus better response to variable demand with equally variable *Vt*. This approach thus provides a patient-specific comparison of which mode better matched *Vt* and *∫Eadi*. Equally, the comparison of Range90 values for a given patient enable one to quantify how much better one mode matched inspiratory demand and resulting tidal volume. Overall, what makes this work and Range90 unique is its patient-specificity, enabling patient-specific comparison where prior works [6-9,15] make comparison on a global or cohort level between modes of ventilation or ventilation strategies.

4.1 Limitations

One possible limitation of this study is the definition of a minimum tidal volume that defines a breath versus an artefact, where those breaths with $Vt<50ml$ were ignored. The selection was made through post hoc analysis of the Vt distribution indicating a bimodal distribution, one mode representing physiological respiratory activity and a small mode ($Vt<50ml$) likely corresponding to artefacts in Eadi. This statement is based on the observation that there was no significant ventilator pressurisation associated with Vt lower than $50ml$. A re-analysis of the data with a limit of $100ml$ showed no change in the overall results, wherein NAVA provided a better match to patient variability in $\int Eadi$ for 21 of 22 patients, and the lower quartile still had a PS/NAVA ratio of 1.40. Thus, the analysis presented is robust to this choice

Range90 only considers the matching of Vt magnitude of a ‘known’ breathing cycle towards the corresponding $\int Eadi$. Thus, if $Vt>50ml$ and $\int Eadi$ exist, it is used, and any asynchrony is seen as a mismatch of the Vt and $\int Eadi$ magnitude. If $Vt<50ml$ and $\int Eadi$ exist, this information is not included. However, 300~500 ‘known’ breathing cycles are analysed for every patient in each ventilation mode. An average of only 30 breaths of ~500 per patient (6%) were discarded in each phase. Thus, the loss of this potential data, assuming they are true breaths, is negligible.

It is important to note that, while Range90 shows better matching in NAVA than PS, it is yet to be applied as a bedside monitoring tool. Range90 in this study used 20 minutes of breathing pattern of a patient in each ventilation mode, and the total duration fort the study is not clinically feasible. In addition, the availability of *Eadi* signal for Range90 analysis is dependent on the availability of NAVA nasogastric tube. This study is a proof of concept and patient respiratory adaptation time to different ventilation mode was taken into consideration [16]. Thus, the results indicate that the use of Range90 as a bedside monitoring tool warrants further investigation with shorter monitoring time.

Another limitation is that setting NAVA gain to obtain similar peak pressure as PS, is an approximation based on the built in previsualisation system and only one NAVA gain value is used to compare with PS. The amplitude of delivered pressure during NAVA is variable, as it is proportional to *Eadi* signal. Therefore, it is possible that the delivered peak pressure may be higher or lower in different patients when comparing PS and NAVA. An online supplement file is included to show peak pressure delivered in different ventilation for every patient. However, it was found that there was no significant difference between peak pressure between these two ventilation modes (P>0.005) as shown in Table 2. Thus, for this cohort of 22 patients, the peak pressure in both modes can be considered as 'similar'.

In this study, only one NAVA level and one PS level was tested and the influence of increasing NAVA level towards *Vt/∫Eadi* was not determined. The effect of *Vt* and *∫Eadi* related to increase in NAVA level have been extensively described by Passath et al [10]. Based on the results, we can assume that increasing NAVA level will result in a consecutive decrease in *Eadi* and in a small and only initial increase in *Vt*. As a consequence, we can assume that with increased NAVA level, *Vt/∫Eadi* ratio will also increase, but this point must be formally explored in future studies to test this hypothesis.

5.0 CONCLUSIONS

Compared to PS, NAVA allowed better match between *Vt* and *Eadi* as well as higher variability in *Vt*. As higher variability has been associated with improved oxygenation and as higher variability is present in healthier systems, the ability of NAVA in not reducing patient's intrinsic variability could be of potential clinical interest. Future work is needed to explore if there was a potential effect of this maintained variability obtained with NAVA on patients' outcome.

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7.0 CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

8.0 LIST OF ABBREVIATION

BMI - Body mass index
CV - Coefficient of variation
CDF - Empirical cumulative distribution function
Eadi - Electrical activity of the diaphragm
$\int Eadi$ - *Eadi* area
ETS - Expiratory trigger sensitivity
FiO_2 - Fraction of inspired oxygen
IQR - Interquartile range
ICU - Intensive care units
NAVA - Neurally adjusted ventilatory assist
PaO_2 - Partial pressure of oxygen in arterial blood
PIP - Peak airway pressure
PS - Pressure Support
SD - Standard deviation
Ti - Inspiratory time
$Ti_{\_Neural}$ - Neural inspiratory time
Vt - Tidal volume

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