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Decreased breathing variability is associated with poorer outcome in mechanically ventilated patients

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"Take home" message: In mechanically ventilated patients studied at the transition from assist-control ventilation to a partial mode of assistance, higher breath-by-breath variability and spectral variability were associated with better outcomes.

Abstract

Rationale. Breathing is a cyclic activity that is by nature variable. Breathing variability is modified in mechanically ventilated (MV) patients.

Objectives. We aimed to evaluate whether decreased variability on the day of transition from assist-control ventilation to a partial mode of assistance was associated with a poorer outcome.

Methods. This was an ancillary study of a multicenter, randomized, controlled trial comparing neurally adjusted ventilatory assist to pressure support ventilation. Flow and the electrical activity of the diaphragm (EAdi) were recorded within 48 hours of switching from controlled ventilation to a partial mode of ventilatory assistance.

Measurements. Variability of flow and EAdi-related variables were quantified by the coefficient of variation, the amplitude ratio of the spectrum's first harmonic to its zero-frequency component (H1/DC) and two surrogates of complexity,.

Main Results. Ninety-eight patients ventilated for a median duration of 5 days were included. H1/DC of inspiratory flow and EAdi were lower in survivors than in non-survivors, suggesting a higher breathing variability in this population (for flow, 37% vs. 45%, p=0.041; for EAdi, 42% vs. 52%, p=0.002). By multivariate analysis, H1/DC of inspiratory EAdi was independently associated with day-28 mortality (odds ratio 1.10, p=0.002). H1/DC of inspiratory EAdi was lower in patients with a duration of MV < 8 days (41% vs. 45%, p=0.022). Noise limit and the largest Lyapunov exponent suggested a lower complexity in patients with a duration of MV < 8 days.

Conclusion. Higher breathing variability and lower complexity are associated with higher survival and lower duration of MV.

Keywords: breathing variability; coefficient of variation; complexity; weaning; mortality.

Introduction

Breathing is a cyclic activity that is not monotonous but exhibits natural variability [1, 2]. In normal human subjects, ventilation shows breath-by-breath variability in descriptors of breathing pattern such as respiratory rate and tidal volume [2]. Breathing variability can also be characterized by the spectral analysis of the flow signal [3, 4]. Finally, breathing activity is also nonlinear in nature and exhibits chaos-like mathematical complexity [5, 6].

In the intensive care unit (ICU), decreased breath-by-breath variability in mechanically ventilated (MV) patients is associated with weaning failure [3, 7], and one study showed that alterations of respiratory rate spectral analysis are associated with increased mortality [5]. However, in this latter study, variability was quantified globally, from the initiation of MV to extubation, which precluded the use of variability as a prognostic index at a given time point of ICU stay. In addition, in these studies, breathing variability was restricted to downstream variables such as airway flow and tidal volume, while the upstream variability of the central inspiratory activity was ignored. It is worth noting that the electromyographic activity of the diaphragm depends directly on the central inspiratory activity [8]. Finally, variability was generally assessed using one single tool of analysis. A recent review also describes breathing variability in anesthesia and critical care, suggesting that variability of respiration is not yet fully understood and that the respiratory system should be measured as a whole rather than a single parameter [9].

Here, we performed an ancillary study of a multicenter, randomized, controlled trial. We described and quantified variability by an array of descriptors, including breath-by-breath variability, spectral analysis and mathematical complexity. This quantification was achieved at the transition between assist-control ventilation and ventilation with a partial mode, in other words as soon as patients could sustain pressure support ventilation. We chose this given time point because this is the first moment during MV that the brain resumes its control over

ventilator activity and therefore the first moment that the natural variability of the respiratory system can be evaluated, since this natural variability was previously occulted by control ventilation [10]. We hypothesized that a low variability at the time of the switch to partial ventilatory mode could predict a poorer outcome.

Methods

This is a preplanned ancillary study of a multicenter, randomized, controlled trial that aimed to compare neurally adjusted ventilatory assist (NAVA) to pressure support ventilation (PSV) in mechanically ventilated patients in 11 ICU departments in France (clinical trial registration number NCT02056093) [11]. The study protocol was approved for all centers by the Comité de Protection des Personnes Ile de France 8 (No. 2010-A00424-35), according to French law. A detailed description of the study design and data from this cohort has been published previously [11, 12].

Patients

Patients receiving MV for more than 24 h for acute respiratory failure of respiratory cause were eligible when they met the following criteria: ability to sustain PSV for at least 30 min with a total level of inspiratory pressure less than 30 cmH_2O, estimated remaining duration of mechanical ventilation greater than 48 h, level of sedation less than or equal to four on the Ramsay scale, fraction of inspired oxygen less than or equal to 50% with a positive end-expiratory pressure less than or equal to 8 cmH_2O and absence of administration of high-dose vasopressor therapy. Exclusion criteria were age below 18, known pregnancy, participation in another trial within the 30 days preceding satisfaction of the eligibility criteria, contraindication of the implementation of the esophageal tube and decision to withhold life-sustaining treatment.

Patient management

After inclusion, patients were connected to a Servo-i ventilator (Maquet Critical Care, Sweden) equipped with NAVA mode. An extensive description of patient management is provided in the Supplemental methods within the Online Supplement

Data collection

Airway pressure, airway flow and EAdi were recorded 12, 24, 36 and 48 hours after inclusion. They were acquired for 20 min at 100 Hertz from the ventilator connected to a computer using commercially available software (Servo-i RCR, version 3.6.2, Maquet Critical Care). Outcome data included mortality 28 days after inclusion, duration of MV and ventilator-free days (VFDs) 28 days after inclusion.

Data analysis

For each patient, the four 20-minute recordings (12, 24, 36 and 48 hours after inclusion) were merged into one single 80-minute recording session on which analyses were performed (Figure 1). An extensive description of signal processing and data analysis is provided in the Supplemental methods within the Online Supplement.

Breath-by-breath variability of flow-derived and EAdi-derived breathing pattern variables was assesses by the coefficient of variation (standard deviation divided by the mean, the higher the coefficient of variation, the higher the variability). Flow-derived breathing pattern variables included tidal volume and respiratory rate. For EAdi, peak EAdi (EAdi-peak) and EAdi-inspiratory neural time were determined.

Spectral-derived variability was assessed using the amplitude ratio of the spectrum's first harmonic (H1) to its zero-frequency or DC component (H1/DC) according to the method described by Gutierrez et al. [4] (the higher the H1/DC, the lower the variability).

Breathing complexity was assessed by the noise limit and largest Lyapunov exponent [13]. A noise limit above zero means nonlinearity and a certain degree of complexity [10, 14,

15]. Sensitivity to initial conditions is how perturbations occurring in the past affect the future behavior of the system and is another characteristic of how a complex system is unpredictable. This was estimated for flow and EAdi using the largest Lyapunov exponent [13].

Statistics

As this is an ancillary study, no sample size could be calculated to detect a difference. The sample size was determined by the parent study [11]. Statistical analysis was performed with GraphPad (GraphPad Software, San Diego, CA, USA) and R (The R Foundation, Vienna, Austria). Continuous data were reported as median (interquartile range) and categorical data as number of events (percentages). Continuous variables (i.e. duration of MV and number of 28-day VFDs) were dichotomized according to their median value in the population.

Differences between groups were assessed with the Mann-Whitney test for continuous variables and with the Chi-2 test for categorical variables. Each potential risk factor for death was first evaluated in a univariate model. Then, a multivariate logistic regression analysis was performed. The multivariate model was built with variables that yielded p values of less than 0.2 on univariate analysis. The adjusted odds ratio (OR) of variables present in the final model is presented with a 95% confidence interval (CI). Finally, correlation between duration of MV, 28-day VFDs and descriptors of breathing variability were evaluated using Spearman's rank correlation coefficient.

Results

Study population

One hundred and twenty-eight patients were included in the parent study, 62 in the NAVA group and 66 in the PSV group. For technical reasons, flow, pressure and EAdi analysis failed in 14 patients of the NAVA group and 16 patients of the PSV group. Subsequently, data on breathing variability were available for 98 patients, 48 in the NAVA

group and 50 in the PSV group. The main characteristics of the patients are displayed in Table 1.

Table SDC1, compares the descriptors of breathing variability between patients assigned to the NAVA group and those assigned to the PSV group in the mother trial. The coefficient of variation of the tidal volume and the LLE for flow were higher in patients assigned to the NAVA group as compared to those assigned to the PSV group.

Association between breathing variability and 28-day mortality

Mortality within 28 days was 19% (n=19). Table 2 shows the descriptors of breathing variability associated with 28-day mortality by univariate analysis. Among descriptors of breathing variability, two differed between survivors and non-survivors. H1/DC of inspiratory flow and H1/DC of inspiratory EAdi were lower in survivors, suggesting a higher variability in this population. By multivariate analysis, H1/DC of inspiratory EAdi was the only factor independently associated with 28-day mortality (OR 1.10, 95% CI 1.04-1.17, p=0.002).

Association between breathing variability and duration of MV

Duration of MV was 8 (4-13) days. Table 3 shows the descriptors of breathing variability associated with duration of MV. Among descriptors of breathing variability, three differed between patients with a duration of MV < 8 days and those with a duration of MV ≥ 8 days. H1/DC of inspiratory EAdi was lower in patients with a duration of MV < 8 days, and there was a significant bur poor-correlation between H1/DC of inspiratory flow and EAdi and duration of MV (Figure SDC1). This suggested a higher breathing variability in patients with a shorter duration of MV. Noise limit for respiratory flow and EAdi was higher in patients with a longer duration of MV, and there was a positive correlation between noise limit for respiratory flow and EAdi and duration of MV. This suggested an association between a higher complexity and a longer duration of MV (Figure SDC1, Table SDC2).

Association between breathing variability and 28-day VFDs

Ventilator-free days 28 days after inclusion were 23 (10-25) days. Table 4 shows the association between descriptors of breathing variability and 28-day VFDs. Among descriptors of breathing variability, eight differed between patients with 28-day VFDs < 23 days and those with 28-day VFDs ≥ 23 days. Among patients with 28-day VFDs ≥ 23 days, the coefficient of variation of the tidal volume was higher and the inspiratory and expiratory H1/DC for EAdi and flow were lower, suggesting an association between a higher variability and an increased number of 28-day VFDs. Correlations between these variables and 28-day VFDs conveyed the same message. Among patients with 28-day VFDs < 23 days, the noise limit of flow and EAdi and de LLE of flow were higher, with a correlation between these variables and 28-day VFDs. These results suggested that a higher complexity was associated with fewer 28-day VFDs (Figure 2, see also Table SDC3).

Discussion

The main findings in our cohort of 98 mechanically ventilated patients studied at the early phase of weaning can be summarized as follows: 1) higher breath-by-breath variability as assessed by the coefficient of variation and higher spectral variability as assessed by the H1/DC ratio were associated with a lower mortality and a lower duration of MV, resulting in increases in VFDs, 2) higher complexity as assessed by noise limit and the largest Lyapunov exponent was associated with a longer duration of MV and fewer VFDs.

To our knowledge, this is the first study to evaluate in a large population the prognostic impact of reduced variability and complexity in the ICU at one given time point (i.e. the transition between assist-control ventilation and a partial mode of assistance such as PSV or NAVA) and with several flow- and EAdi-derived indices to quantify breath-by-breath variability, spectral-derived variability and complexity. Previous studies on this topic used only one of these approaches and did not integrate EAdi into their analyses.

Relationship between variability and outcome

A major result was that higher breath-by-breath and spectral variability were associated with a better outcome. This result is in line with previous reports showing that a higher breath-by-breath variability is associated with a higher weaning success rate [7, 16]. A body of literature suggests an inverse relationship between breathing variability and respiratory system loading [17-19]. In MV patients, unloading the respiratory system is associated with higher respiratory variability [20, 21]. These results suggest that respiratory variability parallels the load-capacity balance of the respiratory system. A high variability may witness a large respiratory reserve [7] and subsequently a higher likeliness to be weaned with, in turn, a shorter duration of mechanical ventilation [22]. Regarding the association between higher spectral variability as assessed by the H1/DC ratio and lower mortality, our findings confirm the previous report from Gutierrez et al. [3].

Relationship between complexity and outcome

Greater complexity was associated with a longer duration of MV and fewer VFDs. Ventilatory flow is not periodic [5] but exhibits complexity, with this term implying irregularity, sensitivity to initial conditions and unpredictability. In other words, this is the amount of “surprise” or “new information” introduced into an otherwise predictable system, i.e. the degree of disorder or randomness in the data [9]. In animals and humans, ventilator complexity has been characterized by various mathematical approaches such as correlation dimension, approximate entropy, Lyapunov exponents and noise limit, which investigates the chaotic nature of ventilator flow [23].

Few studies have evaluated the relationship between complexity and outcome in ICU patients. These studies are in line with our results. The study by El-Khatib et al. showed that the breathing pattern measured by Kolmogorov entropy and respiratory flow-volume phase space dimension during MV was more complex and chaotic in patients who failed weaning

than in those who succeeded [24]. The study by Engoren et al. found similar results. Patients who failed weaning showed increased irregularity in the biosignal analysis of approximate tidal volume entropy, which, according to the authors, reflected enhanced external inputs to the respiratory control center. They suggested that increased regularity in the weaning success group indicated a better adaptive mechanism of an autonomous system [25]. Finally, Park et al. found that the electrocardiogram and photoplethysmography exhibited more complex and chaotic behavior in patients who failed weaning [26].

Clinical implications and perspectives

Our results suggest that breathing variability measured at a given time point, the transition between assist-control ventilation and a partial mode of assistance, could be used as a predictor of duration of MV and even survival. This may help in deciding important therapeutic options such as hastening the weaning process or, conversely, performing a tracheostomy.

It is worth noting that analyses derived from the upstream EAdi signal did not provide much more information than analyses derived from the downstream flow signal, which will simplify the assessment of variability in daily practice, since recording the respiratory flow signal is much easier than recording the EAdi. This result was quite surprising, since EAdi is a closer surrogate of the activity and hence variability of the central respiratory pattern generators located in the brainstem [8]. It suggests that the prognostic value of breathing variability results not only from the central respiratory patter generator from where it originates [23], but also from the way the respiratory system alters this neural variability, which relates to the load-capacity relationship of the respiratory system [17, 18, 27].

Because greater variability is associated with a better outcome, one can hypothesize that restoring variability could improve the outcome. A body of literature suggests that, during

MV, greater variability may be associated with a more protective ventilation. In mechanically ventilated animals, decreased variability of tidal volume is associated with altered lung mechanics and increased lung damage [28], and the restoration of a certain level of variability [29-31] improves respiratory system compliance and the secretion of surfactant, decreases histological lung damage and lung inflammation and improves gas exchange [28-32]. Restoring variability could involve the restoration of the intrinsic variability of the respiratory system with a proportional mode of ventilation such as NAVA or proportional assist ventilation [8, 33]. Previous studies have shown that breath-by-breath variability is higher with these modes than with pressure support ventilation [8, 33]. This could involve the introduction of a certain level of extrinsic variability with modes of mechanical ventilation such as variable or "noisy" pressure support ventilation [34, 35]. In mechanically ventilated patients, this mode is associated with improved gas exchange [22].

From a clinical perspective, our results pave the way of future studies evaluating how breathing variability could be used to improve the management of mechanical ventilation. For instance, combined with other anamnestic or clinical data, breathing variability may help to determine the outcome of a patients transitioning from assist-controlled ventilation to pressure support.

In the era of artificial intelligence and personalized medicine, our results could be later used as a predictive algorithm for weaning success or failure and to adjust the promptness of transition from controlled and assist-controlled ventilation to a partial mode of assistance. In addition, mechanically ventilated patients at high risk of mortality will be more easily identified.

Strength and limitations of the study

The strengths of this study include the unselected character of our population of ICU patients, which is quite representative of a standard ICU population given its characteristics,

severity and outcome. The multicenter design, involving 11 ICUs, enhances the generalizability of our findings. Finally, all the patients were studied at a given and comparable time point. This study presents a number of limitations. First, the sample size was not calculated *a priori* because it was a secondary analysis. Second, the recordings could not be analyzed in some patients, which reduced the sample size and in turn decreased the power of the study. Third, some of the indices we used required long and complex mathematical processing, which limits the immediate transposition of our results. Fourthly, aggregating measurements made over 48 hours could to "dilute" the moment when the brain recovers its aptitude to generate variability. However, limiting the analysis to the first recording would have limited the quality of analyses due to the short duration (20 minutes) of the recording. Finally, our study suggests how to monitor the transition from assist-control ventilation to a partial mode of assistance in a large but heterogeneous population and confounders as disease severity, comorbidities, baseline diagnostics may have impacted the results. Further studies are therefore needed to determine in more balanced groups the impact of our measurements. In this preliminary, and by no means exhaustive, study on the use of an array of variability and complexity descriptors; it would be nice to further compared the analyzed parameters between the different weaning groups (i.e., short, difficult, and prolonged weaning) keeping only the analysis of the significant parameters identified in this work.

Conclusion

In mechanically ventilated patients studied at the transition from assist-control ventilation to a partial mode of assistance, higher breath-by-breath variability and spectral variability were associated with better outcomes. These results pave the way for future studies that will evaluate more precisely the accuracy of these indices, which time point is the more reliable to gather them, and if repeated measures could improve this accuracy. Obviously, these studies will require the development of automated tools. In addition, these results

support trials that would evaluate the prognostic impact of strategies aiming at restoring a more physiologic level of variability in mechanically ventilated patients, although this physiological level is yet unknown [2, 36].

Figure legends

Figure 1. Experimental design.

Abbreviation: EAdi, electrical activity of the diaphragm; PSV, pressure support ventilation; NAVA, neurally adjusted ventilatory assist; H1/DC, amplitude ratio of the first harmonic peak (H1) to that of zero frequency (also termed DC component).

Figure 2. Correlation between 28-day ventilator-free days (VFDs) and descriptors of breathing variability (A) coefficient of variation of Tidal volume (%), (B) H1/DC inspiratory flow, *%*, (C) H1/DC inspiratory EAdi, *%*, (D) H1/DC expiratory flow, *%*, (E) H1/DC expiratory EAdi, *%*, (F) Noise Limit flow, *%*, (G) Noise Limit EAdi, *%*, (H) LLE flow, $bit.iteration^{-1}$ evaluated using Spearman's rank correlation coefficient.

Abbreviation: EAdi, electrical activity of the diaphragm; H1/DC, amplitude ratio of the first harmonic peak (H1) to that of zero frequency (also termed DC component).

Tables

Table 1. Baseline characteristics of the patients

	n=98
Gender male, *n (%)*	65 (66)
Age, *year*	68 (60-77)
SAPS 2	44 (34-59)
Charlson score	3 (2-5)
ATICE	16 (11-19)
Duration of controlled or assist-controlled ventilation prior to switch to partial mode, *days*	5 (3-9)
Duration of mechanical ventilation, *days*	8 (4-13)
Ventilator-free days 28 days after inclusion, *days*	23 (10-25)
Mortality within 28 days, *n (%)*	19 (19)
Cause of acute respiratory failure	
De novo ARF, *n (%)*	57 (58)
Post-operative ARF, *n (%)*	19 (19)
Acute-on-chronic ARF, *n (%)*	17 (18)
Acute cardiogenic pulmonary edema, *n (%)*	5 (5)
Ventilator measurements, *at inclusion*	
PEEP, cmH_2O	6 (5-8)
PSV level[a], cmH_2O	12 (10-13)
NAVA level[b], $cmH2O,\mu V^{-1}$	1.6 (1.2-2.3)
Breathing pattern, *at inclusion*	
Tidal volume, *ml*	450 (400-525)
Respiratory rate, min^{-1}	24 (20-29)
Minute ventilation, l,min^{-1}	11 (9-13)
Blood gases	
PaO_2/FiO_2 at inclusion, *mmHg*	240 (193-286)
$PaCO_2$ at inclusion, *mmHg*	40 (35-48)

SAPS, simplified acute physiology score; ATICE, adaptation to the intensive care environment; ARF, acute respiratory failure; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; NAVA, neurally adjusted ventilatory assist.

Continuous data are reported as median (interquartile range) and categorical data as number of events (percentages).

[a]PSV level is reported for the 50 patients mechanically ventilated with the PSV mode.

[b]NAVA level is reported for the 48 patients mechanically ventilated with the NAVA mode.

Table 2. Association between descriptors of breathing variability and 28-day mortality

	Survivors n=79	Non survivors n=19	p
Baseline characteristics of the patients			
Gender male, n (%)	51 (65)	14 (74)	0.408
Age, *years*	66 (58-76)	75 (69-79)	0.015
SAPS 2	42 (33-54)	48 (42-67)	0.016
Charlson score	4 (2-5)	3 (2-4)	0.174
ATICE	16 (11-19)	14 (10-19)	0.304
Duration of MV prior to inclusion, *days*	5 (2-9)	6 (3-9)	0.751
Cause of acute respiratory failure			
De novo ARF, *n (%)*	45 (57)	12 (63)	0.596
Post-operative ARF, *n (%)*	16 (20)	3 (16)	1
Acute-on-chronic ARF, *n (%)*	14 (18)	3 (16)	1
Acute cardiogenic pulmonary edema, *n (%)*	4 (5)	1 (5)	1
Ventilator measurements, *at inclusion*			
PEEP, cmH_2O	6 (5-8)	8 (6-8)	0.031
PSV level[a], cmH_2O	12 (10-12)	14 (8-17)	0.611
NAVA level[b], $cmH2O,\mu V^{-1}$	1.6 (1.2-2.3)	1.9 (1.4-2.3)	0.481
Breathing pattern, *at inclusion*			
Tidal volume, *ml*	440 (400-520)	445 (381-541)	0.932
Respiratory rate, min^{-1}	24 (20-29)	26 (20-29)	0.635
Minute ventilation, l,min^{-1}	11 (9-13)	12 (10-14)	0.285
Blood gases			
PaO_2/FiO_2 at inclusion, *mmHg*	240 (195-292)	226 (186-264)	0.355
$PaCO_2$ at inclusion, *mmHg*	39 (34-45)	41 (35-51)	0.442
Descriptors of breathing variability			
Coefficient of variation			
Tidal volume, *%*	22 (16-34)	21 (14-25)	0.150
Respiratory rate, *%*	23 (18-30)	22 (14-26)	0.263
EAdi-peak, *%*	34 (27-46)	35 (24-46)	0.754
EAdi-inspiratory neural time, *%*	31 (27-38)	31 (23-52)	0.864
H1/DC			
Inspiratory flow, *%*	37 (31-44)	45 (33-52)	0.041
Inspiratory EAdi , *%*	42 (34-48)	52 (41-58)	0.002
Expiratory flow, *%*	23 (18-30)	24 (19-31)	0.614
Expiratory EAdi, *%*	30 (24-35)	34 (29-36)	0.091
Complexity			
Noise limit, flow, *%*	46 (33-65)	50 (38-82)	0.241
Noise limit, EAdi, *%*	45 (34-66)	51 (37-83)	0.384
LLE, flow, $bit.iteration^{-1}$	2.15 (1.61-2.65)	2.32 (1.84-2.54)	0.583
LLE, EAdi, $bit.iteration^{-1}$	0.21 (0.11-0.34)	0.19 (0.11-0.49)	0.793

SAPS, simplified acute physiology score; ATICE, adaptation to the intensive care environment; ARF, acute respiratory failure; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; NAVA, neurally adjusted ventilatory assist. EAdi, electrical activity of the diaphragm; H1/DC, amplitude ratio of the first harmonic peak (H1) to that of zero frequency (also termed DC component); LLE, largest Lyapunov exponent.

Continuous data are reported as median (interquartile range) and categorical data as number of events (percentages).

[a]PSV level is reported for the 50 patients mechanically ventilated with the PSV mode.

[b]NAVA level is reported for the 48 patients mechanically ventilated with the NAVA mode.

Table 3. Association between descriptors of breathing variability and duration of mechanical ventilation (MV)

	Duration of MV < 8 days n = 49	Duration of MV ≥ 8 days n = 49	p
Baseline characteristics of the patients			
Gender male, n (%)	32 (65)	33 (67)	0.831
Age, *years*	68 (57-77)	66 (61-77)	0.507
SAPS 2	37 (31-49)	44 (39-44)	0.021
Charlson score	5 (3-6)	5 (4-6)	0.466
ATICE	16 (11-19)	15 (11-18)	0.549
Duration of MV prior to inclusion, *days*	5 (2-8)	7 (4-10)	0.259
Cause of acute respiratory failure			
De novo ARF, *n (%)*	28 (59)	26 (54)	0.684
Post-operative ARF, *n (%)*	11 (21)	9 (18)	0.616
Acute-on-chronic ARF, *n (%)*	6 (12)	10 (20)	0.274
Acute cardiogenic pulmonary edema, *n*	4 (8)	4 (8)	1
Ventilator measurements, *at inclusion*			
PEEP, cmH_2O	6 (5-8)	7 (5-8)	0.384
PSV level[a], cmH_2O	12 (10-12)	12 (10-16)	0.182
NAVA level[b], *cmH2O,µV-1*	1.6 (1.2-2.0)	1.9 (1.2-2.3)	0.403
Breathing pattern			
Tidal volume, *ml*	440 (400-511)	445 (385-547)	0.882
Respiratory rate, min^{-1}	23 (18-30)	24 (21-28)	0.918
Minute ventilation, l,min^{-1}	11 (9-13)	11 (9-13)	0.926
Blood gases			
PaO_2/FiO_2 at inclusion, *mmHg*	251 (207-317)	213 (185-266)	0.021
Mean PaO_2/FiO_2 , *mmHg*	228 (167-314)	214 (174-266)	0.347
$PaCO_2$ at inclusion, *mmHg*	39 (34-44)	41 (35-48)	0.204
Descriptors of breathing variability			
Coefficient of variation			
Tidal volume, *%*	24 (16-34)	19 (15-30)	0.113
Respiratory rate, *%*	23 (19-30)	22 (17-29)	0.378
EAdi-peak, *%*	35 (27-47)	34 (27-46)	0.864
EAdi-inspiratory neural time, *%*	31 (27-39)	31 (26-42)	0.963
H1/DC			
inspiratory flow, *%*	37 (30-42)	39 (34-50)	0.071
inspiratory EAdi , *%*	41 (31-48)	45 (39-52)	0.022
expiratory flow, *%*	23 (17-31)	23 (20-30)	0.684
expiratory EAdi, *%*	30 (24-35)	31 (25-36)	0.318
Complexity			
Noise limit. flow, *%*	42 (31-61)	56 (39-68)	0.006
Noise limit. EAdi, *%*	41 (31-60)	56 (41-70)	0.008
LLE, flow, $bit.iteration^{-1}$	2.1 (1.6-2.6)	2.3 (1.6-2.7)	0.453
LLE, EAdi, $bit.iteration^{-1}$	0.21 (0.11-0.38)	0.21 (0.14-0.33)	0.774

SAPS, simplified acute physiology score; ATICE, adaptation to the intensive care environment; ARF, acute respiratory failure; PEEP, positive end-expiratory pressure; PSV,

pressure support ventilation; NAVA, neurally adjusted ventilatory assist. EAdi, electrical activity of the diaphragm; H1/DC, amplitude ratio of the first harmonic peak (H1) to that of zero frequency (also termed DC component); LLE, largest Lyapunov exponent.

Continuous data are reported as median (interquartile range) and categorical data as number of events (percentages).

[a]PSV level is reported for the 50 patients mechanically ventilated with the PSV mode.

[b]NAVA level is reported for the 48 patients mechanically ventilated with the NAVA mode.

Table 4. Association between descriptors of breathing variability and 28-day ventilator free days (VFDs)

	28-day VFDs < 23 days n = 49	**28-day VFDs ≥ 23 days n = 49**	**p**
Baseline characteristics of the patients			
Gender male, n (%)	36 (74)	29 (59)	0.558
Age, *years*	72 (63-78)	64 (57-74)	0.031
SAPS 2	48 (40-63)	35 (26-45)	<0.0001
Charlson score	5 (4-7)	5 (4-6)	0.285
ATICE	15 (11-19)	16 (11-18)	0.194
Duration of MV prior to inclusion, *days*	6 (3-9)	5(1-14)	0.897
Cause of acute respiratory failure			
De novo ARF, *n (%)*	31 (64)	23 (47)	0.154
Post-operative ARF, *n (%)*	8 (16)	12 (25)	0.452
Acute-on-chronic ARF, *n (%)*	7 (14)	9 (18)	0.785
Acute cardiogenic pulmonary edema, *n*	3 (6)	5 (10)	0.714
Ventilator measurements, *at inclusion*			
PEEP, cmH_2O	6 (5-8)	7 (5-8)	0.850
PSV level[a], cmH_2O	12 (11-16)	11(10-12)	0.040
NAVA level[b], *cmH2O,µV-1*	1.8 (1.2-2.3)	1.6 (1.1-2)	0.452
Breathing pattern			
Tidal volume, *ml*	440 (400-547)	450 (398-518)	0.954
Respiratory rate, min^{-1}	24 (22-29)	23 (18-27)	0.094
Minute ventilation, l,min^{-1}	11 (10-14)	10 (8-12)	0.041
Blood gases			
PaO_2/FiO_2 at inclusion, *mmHg*	225 (184-266)	249 (202-298)	0.044
Mean PaO_2/FiO_2 , *mmHg*	214 (176-253)	231 (164-316)	0.388
$PaCO_2$ at inclusion, *mmHg*	40 (35-45)	40 (34-48)	0.951
Descriptors of breathing variability			
Coefficient of variation			
Tidal volume, *%*	19 (14-28)	25 (17-36)	0.023
Respiratory rate, *%*	22 (16-26)	24 (19-30)	0.071
EAdi-peak, *%*	32 (26-45)	37 (30-49)	0.087
EAdi-inspiratory neural time, *%*	30 (23-42)	33 (28-39)	0.327
H1/DC			
inspiratory flow, *%*	42 (37-52)	34 (29-41)	<0.0001
inspiratory EAdi , *%*	47 (41-58)	38 (30-46)	<0.0001
expiratory flow, *%*	24 (21-32)	22 (16-28)	0.007
expiratory EAdi, *%*	33 (28-37)	26 (23-33)	0.0002
Complexity			
Noise limit. flow, *%*	52 (40-73)	41 (31-60)	0.012
Noise limit. EAdi, *%*	53 (40-73)	42 (31-60)	0.013
LLE, flow, $bit.iteration^{-1}$	2.32 (1.85-2.78)	2.00 (1.54-2.51)	0.028
LLE, EAdi, $bit.iteration^{-1}$	0.22 (0.12-0.39)	0.20 (0.11-0.31)	0.323

SAPS, simplified acute physiology score; ATICE, adaptation to the intensive care environment; ARF, acute respiratory failure; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; NAVA, neurally adjusted ventilatory assist. EAdi, electrical activity of the diaphragm; H1/DC, amplitude ratio of the first harmonic peak (H1) to that of zero frequency (also termed DC component); LLE, largest Lyapunov exponent.

Continuous data are reported as median (interquartile range) and categorical data as number of events (percentages).

[a]PSV level is reported for the 50 patients mechanically ventilated with the PSV mode.

[b]NAVA level is reported for the 48 patients mechanically ventilated with the NAVA mode.

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Figure 1.

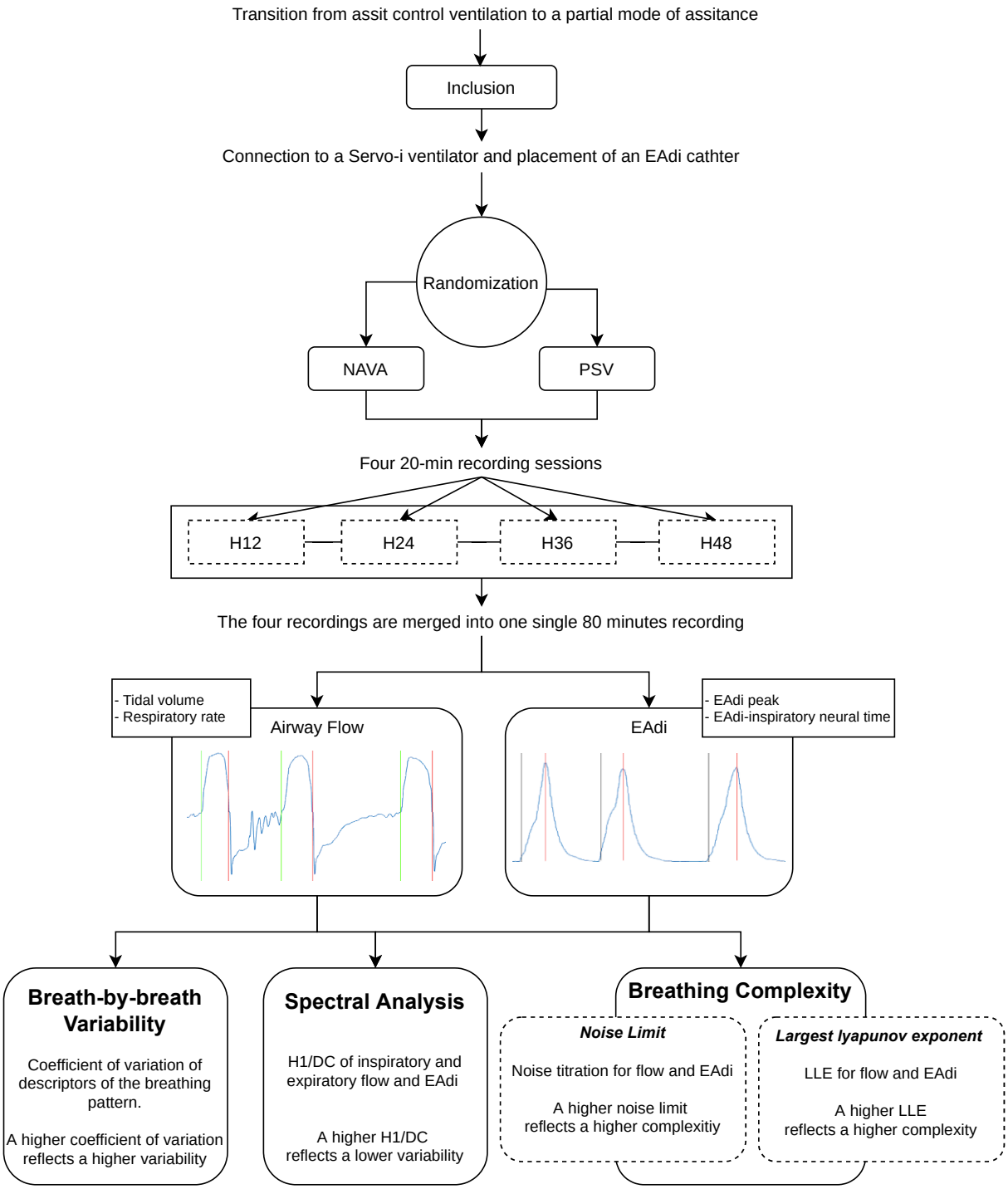
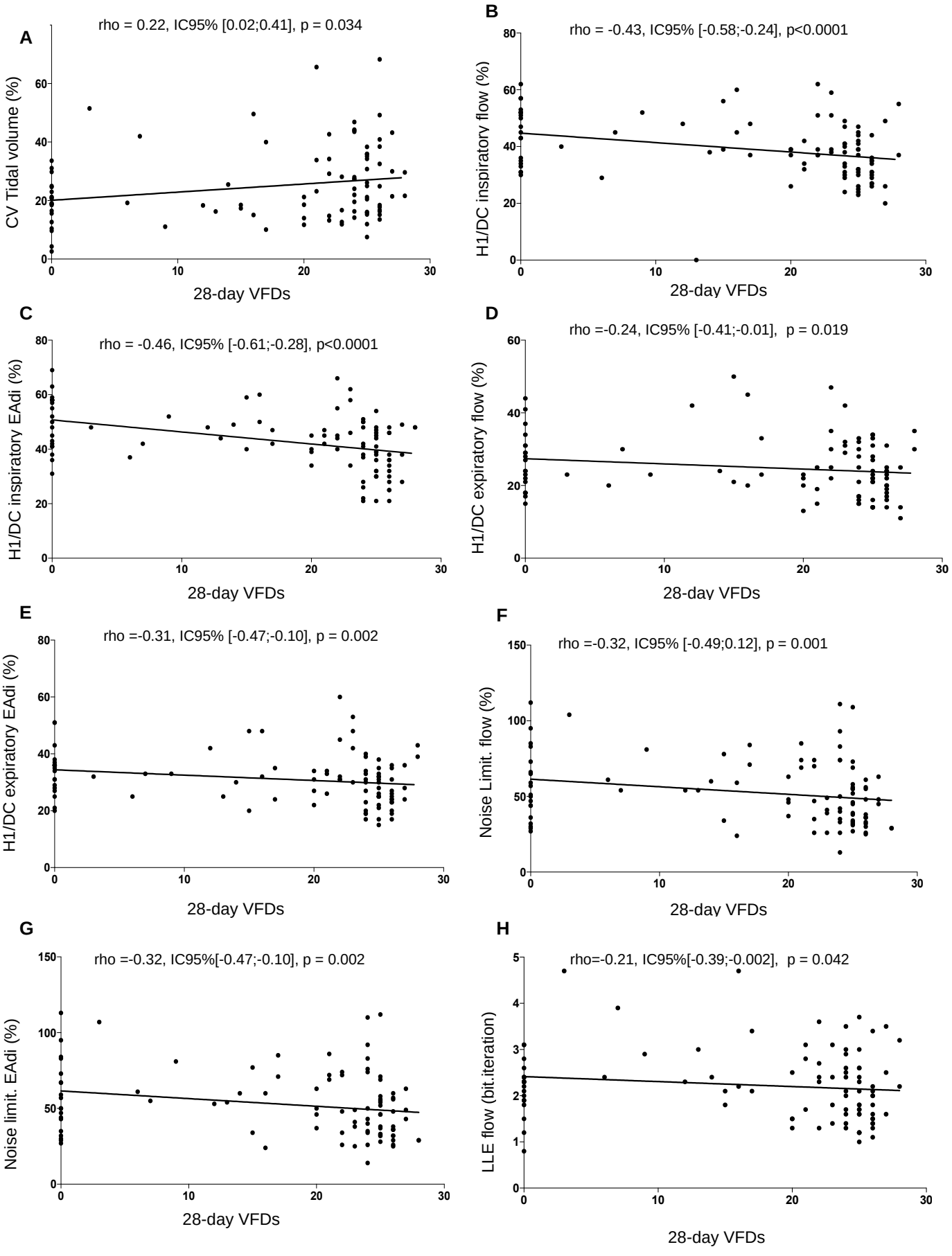

Transition from assit control ventilation to a partial mode of assitance
Inclusion
Connection to a Servo-i ventilator and placement of an EAdi cathter
Randomization
NAVA
PSV
Four 20-min recording sessions
H12
H24
H36
H48
The four recordings are merged into one single 80 minutes recording
- Tidal volume
- Respiratory rate
Airway Flow
EAdi
- EAdi peak
- EAdi-inspiratory neural time
Breath-by-breath Variability
Coefficient of variation of descriptors of the breathing pattern.
A higher coefficient of variation reflects a higher variability
Spectral Analysis
H1/DC of inspiratory and expiratory flow and EAdi
A higher H1/DC reflects a lower variability
Breathing Complexity
Noise Limit
Noise titration for flow and EAdi
A higher noise limit reflects a higher complexitiy
Largest lyapunov exponent
LLE for flow and EAdi
A higher LLE reflects a higher complexity

Figure 2.


A
rho = 0.22, IC95% [0.02;0.41], p = 0.034
CV Tidal volume (%)
28-day VFDs
B
rho = -0.43, IC95% [-0.58;-0.24], p<0.0001
H1/DC inspiratory flow (%)
28-day VFDs
C
rho = -0.46, IC95% [-0.61;-0.28], p<0.0001
H1/DC inspiratory EAdi (%)
28-day VFDs
D
rho =-0.24, IC95% [-0.41;-0.01], p = 0.019
H1/DC expiratory flow (%)
28-day VFDs
E
rho =-0.31, IC95% [-0.47;-0.10], p = 0.002
H1/DC expiratory EAdi (%)
28-day VFDs
F
rho =-0.32, IC95% [-0.49;0.12], p = 0.001
Noise Limit. flow (%)
28-day VFDs
G
rho =-0.32, IC95%[-0.47;-0.10], p = 0.002
Noise limit. EAdi (%)
28-day VFDs
H
rho=-0.21, IC95%[-0.39;-0.002], p = 0.042
LLE flow (bit.iteration)
28-day VFDs

Decreased breathing variability is associated with poorer outcome in mechanically ventilated patients

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Supplementary material

Supplemental methods

Written informed consent was obtained from the patients, or their surrogates, before being included in the study.

Patients

Patients receiving MV for more than 24 h for acute respiratory failure of respiratory cause (*de novo* hypoxemic respiratory failure, acute cardiogenic pulmonary edema or acute-on-chronic respiratory failure) were eligible when they met the following criteria: ability to sustain PSV for at least 30 min with a total level of inspiratory pressure less than 30 cmH_2O, estimated remaining duration of mechanical ventilation greater than 48 h, level of sedation less than or equal to four on the Ramsay scale, fraction of inspired oxygen less than or equal to 50% with a positive end-expiratory pressure less than or equal to 8 cmH_2O and absence of administration of high-dose vasopressor therapy.

Patient management

As soon as they were included, patients were connected to a Servo-i ventilator (Maquet Critical Care, Sweden) equipped with NAVA mode. The standard nasogastric feeding tube was removed and replaced by an electrical activity of the diaphragm (EAdi) catheter consisting of a 16-Fr gastric tube equipped with electrodes. Patients were then randomly assigned to receive either PSV or NAVA. The pressure support level in the PSV group and the NAVA level were set to obtain a tidal volume of 6 to 8 ml/kg of ideal body weight. NAVA or PSV was continued unless the patients met predefined criteria for switching back to controlled mechanical ventilation or for weaning and subsequent extubation. The investigators were not involved in any clinical decisions.

Data collection

Data analysis

For each patient, the four 20-minute recordings (12, 24, 36 and 48 hours after inclusion) were merged into one single 80-minute recording session on which analyses were performed (Figure 1).

Breath-by-breath variability

Flow and EAdi-derived breathing pattern variables were determined on a breath-by-breath basis using a MATLAB script (Mathworks, Natick, MA, USA). This automatic verification was followed by a visual inspection of the recording by two investigators. Flow-derived breathing pattern variables included tidal volume and respiratory rate. For EAdi, peak EAdi (EAdi-peak) and EAdi-inspiratory neural time were measured. The coefficient of variation (standard deviation divided by the mean) was then calculated (the higher the coefficient of variation, the higher the variability).

Spectral analysis

We assessed spectral-derived variability using the amplitude ratio of the spectrum's first harmonic (H1) to its zero-frequency or DC component (H1/DC) according to the method described by Gutierrez et al. [1] (the higher the H1/DC, the lower the variability). H1/DC was calculated for the flow and the EAdi signal. For inspiratory H1/DC, flow expiratory values were set to zero. For expiratory H1/DC, flow inspiratory values were set to zero. This resulted in a periodic, continuous signal, displaying only either the inspiratory or expiratory phase of the cycle. A frequency spectrum was generated by applying the Cooley-Tukey Fast Fourier Transform algorithm [2] to the modified signal data encompassed by a predetermined time window of constant duration. The length of the time window was mandated by the Fast Fourier Transform requirement of 2n samples per frequency spectrum. In order to fit with Gutierrez's method, we chose 4096 (2^{12}) samples, resulting in a time window of 0.7 min at

sampling rate of 100 Hz. The resulting spectrum had a frequency resolution of 24.41 x 10^{-3} Hz. For each spectrum, the H1/DC was calculated with a peak detection algorithm. The same procedure was applied to the EAdi signal.

Breathing complexity

In humans, ventilatory flow is not a truly periodic phenomenon. Its variability from breath to breath exhibits chaos-like mathematical complexity [3]. This means that the trajectory of ventilatory flow is nonlinear, bounded, and not predictable in the long term. As previously described by our group, we carried out complexity analysis of continuous oscillatory signals (flow and EAdi). Consecutive breaths are described in terms of an ensemble of signal trajectories. If only one trajectory is possible, as in a truly periodic system, complexity is minimal, and all breaths should be identical.

After subsampling the signal at 5 Hertz, the noise titration procedure was performed as described previously [4-6], first ascertains the presence of nonlinearity in the signal through a statistical process, and then it quantifies the amount of added white noise needed to mask this nonlinearity. A noise limit above 0 means nonlinearity and a certain degree of chaos-compatible complexity.

Complex dynamical systems exhibit unpredictable behaviors such that small variances in the initial conditions could have profound and widely divergent effects on the system's outcomes. We quantified the sensitivity to initial conditions for flow and EAdi using the largest Lyapunov exponent (LLE), which increases, as the system is more sensitive to initial conditions [7], which increases, as the system is more sensitive to initial conditions.

Statistics

As this is an ancillary study, no sample size could be calculated to detect a difference. The sample size was determined by the parent study [8]. Statistical analysis was performed with GraphPad (GraphPad Software, San Diego, CA, USA) and R (The R Foundation, Vienna, Austria). Continuous data were reported as median (interquartile range) and categorical data as number of events (percentages). Continuous variables (i.e. duration of MV and number of 28-day VFDs) were dichotomized according to their median value in the population.

Differences between groups were assessed with the Mann-Whitney test for continuous variables and with the Chi-2 test for categorical variables. Each potential risk factor for death was first evaluated in a univariate model. Then, a multivariate logistic regression analysis was performed. The multivariate model was built with variables that yielded p values of less than 0.2 on univariate analysis. The adjusted odds ratio (OR) of variables present in the final model is presented with a 95% confidence interval (CI). Finally, correlation between duration of MV, 28-day VFDs and descriptors of breathing variability were evaluated using Spearman's rank correlation coefficient.

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Table SDC1. Differences of descriptors of breathing variability and complexity between ventilator modes

	PSV	NAVA	p
Coefficient of variation			
Tidal volume, *%*	18 (15-25)	28 (19-36)	0.0014
Respiratory rate, *%*	22 (18-30)	23 (18-28)	0.9162
EAdi-peak, *%*	36 (30-52)	34 (25-44)	0.1912
EAdi–inspiratory neural time, *%*	31 (26-39)	32 (27-41)	0.7850
H1/DC			
Inspiratory flow, *%*	37 (31-41)	40 (32-48)	0.2280
Inspiratory EAdi, *%*	39 (33-48)	46 (41-50)	0.0316
Expiratory flow, *%*	23 (18-28)	24 (18-32)	0.4015
Expiratory EAdi, *%*	27 (22-33)	33 (28-38)	0.0015
Complexity			
Noise Limit flow, *%*	46 (34-63)	53 (36-70)	0.2294
Noise Limit EAdi, *%*	46 (34-64)	52 (35-71)	0.2469
LLE flow, $bit.iteration^{-1}$	1.7 (1.4-2.3)	2.5 (2.1-3.1)	<0.0001
LLE EAdi, $bit.iteration^{-1}$	0.20 (0.1-0.4)	0.21 (0.14-0.33)	0.6570

EAdi, electrical activity of the diaphragm; H1/DC, amplitude ratio of the first harmonic peak (H1) to that of zero frequency or DC component; LLE, largest Lyapunov exponent.

Table SDC2. Association between descriptors of breathing variability and complexity, and duration of mechanical ventilation

	Duration of mechanical ventilation		
	Spearman	**IC95%**	**p**
Coefficient of variation			
Tidal volume, *%*	-0.17	[-0.37;0.04]	0.099
Respiratory rate, *%*	-0.06	[-0.28;0.15]	0.542
EAdi-peak, *%*	-0.12	[-0.32;0.09]	0.272
EAdi–inspiratory neural time, *%*	-0.05	[-0.25;0.16]	0.641
H1/DC			
Inspiratory flow, *%*	0.23	[0.02;0.41]	0.030
Inspiratory EAdi, *%*	0.27	[0.07;0.45]	0.008
Expiratory flow, *%*	0.07	[-0.16;0.26]	0.493
Expiratory EAdi, *%*	0.13	[-0.11;0.32]	0.216
Complexity			
Noise Limit flow, *%*	0.25	[0.04;0.43]	0.015
Noise Limit EAdi, *%*	0.25	[0.04;0.42]	0.018
LLE flow, $bit.iteration^{-1}$	0.08	[-0.13;0.27]	0.439
LLE EAdi, $bit.iteration^{-1}$	0.06	[-0.15;0.26]	0.560

EAdi, electrical activity of the diaphragm; H1/DC, amplitude ratio of the first harmonic peak (H1) to that of zero frequency or DC component; LLE, largest Lyapunov exponent.

Table SDC3. Association between descriptors of breathing variability and complexity, and 28-days ventilator-free days

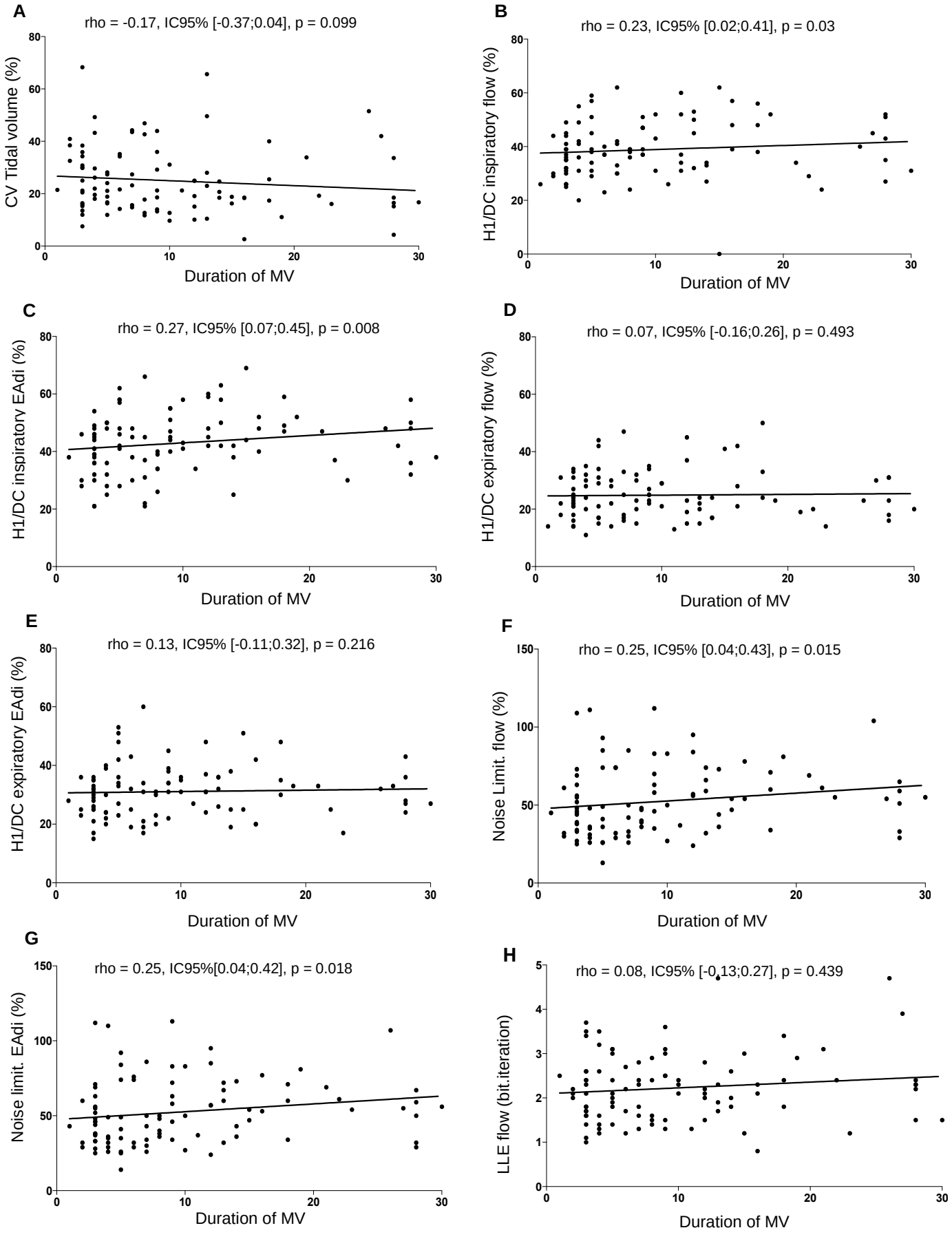
	28-days ventilator-free days		
	Spearman	**IC95%**	**p**
Coefficient of variation			
Tidal volume, *%*	0.22	[0.02;0.41]	0.034
Respiratory rate, *%*	0.19	[-0.03;0.38]	0.076
EAdi-peak, *%*	0.12	[-0.09;0.32]	0.244
EAdi–inspiratory neural time, *%*	0.03	[-0.18;0.24]	0.773
H1/DC			
Inspiratory flow, *%*	-0.43	[-0.58;-0.24]	p<0.0001
Inspiratory EAdi, *%*	-0.46	[-0.61;-0.28]	p<0.0001
Expiratory flow, *%*	-0.24	[-0.41;-0.01]	0.019
Expiratory EAdi, *%*	-0.31	[-0.47;-0.10]	0.002
Complexity			
Noise Limit flow, *%*	-0.32	[-0.49;0.12]	0.001
Noise Limit EAdi, *%*	-0.32	[-0.47;0.10]	0.002
LLE flow, $bit.iteration^{-1}$	-0.21	[-0.39;-0.002]	0.042
LLE EAdi, $bit.iteration^{-1}$	0.02	[-0.18;0.23]	0.818

EAdi, electrical activity of the diaphragm; H1/DC, amplitude ratio of the first harmonic peak (H1) to that of zero frequency or DC component; LLE, largest Lyapunov exponent.

Figure SDC1. Correlation between the duration of mechanical ventilation (MV) and descriptors of breathing variability (A) coefficient of variation of Tidal volume (%), (B) H1/DC inspiratory flow, *%*, (C) H1/DC inspiratory EAdi, *%*, (D) H1/DC expiratory flow, *%*, (E) H1/DC expiratory EAdi, *%*, (F) Noise Limit flow, *%*, (G) Noise Limit EAdi, *%*, (H) LLE flow, $bit.iteration^{-1}$ evaluated using Spearman's rank correlation coefficient.

Abbreviation: EAdi, electrical activity of the diaphragm; H1/DC, amplitude ratio of the first harmonic peak (H1) to that of zero frequency (also termed DC component).

Figure SDC1.


A
rho = -0.17, IC95% [-0.37;0.04], p = 0.099
CV Tidal volume (%)
Duration of MV
B
rho = 0.23, IC95% [0.02;0.41], p = 0.03
H1/DC inspiratory flow (%)
Duration of MV
C
rho = 0.27, IC95% [0.07;0.45], p = 0.008
H1/DC inspiratory EAdi (%)
Duration of MV
D
rho = 0.07, IC95% [-0.16;0.26], p = 0.493
H1/DC expiratory flow (%)
Duration of MV
E
rho = 0.13, IC95% [-0.11;0.32], p = 0.216
H1/DC expiratory EAdi (%)
Duration of MV
F
rho = 0.25, IC95% [0.04;0.43], p = 0.015
Noise Limit. flow (%)
Duration of MV
G
rho = 0.25, IC95%[0.04;0.42], p = 0.018
Noise limit. EAdi (%)
Duration of MV
H
rho = 0.08, IC95% [-0.13;0.27], p = 0.439
LLE flow (bit.iteration)
Duration of MV