Interventions Relieving Dyspnea in Intubated Patients Show Responsiveness of the Mechanical Ventilation - Respiratory Distress Observation Scale

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Thomas Similowski reports personal fees for consulting and teaching activities from ADEP Assistance, AstraZeneca France, Chiesi France, KPL consulting, Lungpacer Inc., OSO-AI, TEVA France, Vitalaire.

Alexandre Demoule reports personal fees from Medtronic, grants, personal fees and non-financial support from Philips, personal fees from Baxter, personal fees from Hamilton, personal fees and non-financial support from Fisher & Paykel, grants from French Ministry of Health, personal fees from Getinge, grants and personal fees from Respinor, grants and non-financial support from Lungpacer, outside the submitted work.

Mathieu Raux has a patent titled *"Dispositif de détection d'un réglage inapproprié d'une machine d'assistance ventilatoire utilisée sur un mammifère" (WO200800696 3A2),* a patent titled *"Détection électroencéphalographique d'une inadéquation entre l'état d'un patient placé sous assistance ventilatoire et réglage de la machine utilisée pour cette assistance" (EP2590701A),* and a patent titled *"Procédé de caractérisation de l'état physiologique d'un patient à partir de l'analyse de son activité électrique cérébrale, et dispositif de surveillance faisant application" (WO2013164462A1),* possibly relevant to some apsects of the preent study.

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Running title

Dyspnea in noncommunicative intubated patients

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Conception and design: MD, CB, SC, MCN, IR, TS, AD

Data acquisition: MD, CB, SC, MCN, JM, EM

Analysis and interpretation: MD, CB, SC, MF, TS, AD

Drafting the manuscript: MD, IR, TS, AD

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At a Glance Commentary

Current scientific knowledge on the subject: To be treated, dyspnea need to be detected, but more than half of intubated critically ill patient are unable to self-report their suffering.

What this study adds to the field: The The Mechanical Ventilation - Respiratory Distress Obervation Scale (MV-RDOS) is associated with neural drive to breath, brain cortical activity changes and is responsive to dyspnea relieving interventions in both communicative and noncommunicative intubated patients.

The MV – RDOS seems able to infer and monitor dyspnea reasonably well in noncommunicative intubated patients.

Online data supplement

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

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Abstract (249 words)

Introduction: Breathing difficulties are highly stressful. In critically ill patients, they are associated with an increased risk of post-traumatic manifestations. Dyspnea, the corresponding symptom, cannot be directly assessed in noncommunicative patients. This difficulty can be circumvented using observation scales such as the mechanical ventilation - respiratory distress observation scale (MV-RDOS). We investigated the performance and responsiveness of the MV-RDOS, to infer dyspnea in intubated noncommunicative patients.

Patients and methods: Communicative and noncommunicative patients exhibiting breathing difficulties under mechanical ventilation were prospectively included and assessed using a dyspnea visual analog scale, MV-RDOS, electromyographic activity of alae nasi and parasternal intercostals and electroencephalographic signatures of respiratory-related cortical activation (pre-inspiratory potentials). Both inspiratory muscles electromyographic and pre-inspiratory cortical activities are surrogate of dyspnea. Assessments were conducted at baseline, after adjustment of ventilator settings, and, in some cases, after morphine administration.

Results: Fifty patients (age: 67 [61-76] years, Simplified Acute Physiology Score II: 52 [35-62]) were included, 25 of whom noncommunicative. Relief occurred in 25 (50%) patients after ventilator adjustments and in 21 additional patients after morphine administration. In noncommunicative patients, MV-RDOS decreased from 5.5 [4.2–6.6] at baseline to 4.2 [2.1–

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4.7] ($p<0.001$) after ventilator adjustments and to 2.5 [2.1-4.2] ($p=0.024$) after morphine administration. MV-RDOS and alae nasi/parasternal electromyographic activities were positively correlated (Rho=0.41 and 0.37, respectively). MV-RDOS was higher in patients with electroencephalographic pre-inspiratory potentials (4.9 [4.2–6.3] vs. 4.0 [2.1–4.9], $p=0.002$).

Conclusion: The MV – RDOS seems able to detect and monitor respiratory suffering reasonably well in noncommunicative intubated patients.

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Introduction

Dyspnea is the most distressing situations that can be experienced by intensive care unit (ICU) patients receiving mechanical ventilation [1]. Reported by almost 50% of the intubated patients who can communicate with their caregivers [2] dyspnea is associated with immediate suffering, anxiety, increased duration of weaning [2] and independently predict the onset of post-traumatic stress disorder in survivors [3]. For these reasons, dyspnea identification and management must be a priority in ICU patients [4], in the same way as pain relief [5].

The identification of dyspnea by caregivers requires the ability of self-report by the patient [6]. In the ICU, self-reporting capabilities are altered in many patients. This is the case in more than 50% of intubated patients [1, 3, 7] in whom endotracheal prostheses, delirium, or sedative drugs all interfere with stakeholder communication. In addition, doctors and nurses underestimate dyspnea in critically ill patients [8-9]. This adds a feeling of helplessness [10, 11] and loss of control to the patient's distress [12], a catastrophic combination that inevitably accentuates anxiety and predisposes to post-traumatic stress disorders [3]. The impossibility for a patient to report dyspnea verbally or gesturally does not negate the possibility for this patient to experience suffering from breathing difficulties. Yet, the brain reactions triggered by respiratory abnormalities have other manifestations than dyspnea. These manifestations can be captured by so-called "observation scales" such as the respiratory distress observation scale (RDOS) [13]. The RDOS takes into account physical signs related to increased breathing drive (e.g. breathing rate, activation of accessory inspiratory muscles), to neurovegetative reaction (e.g. heart rate) and to psychological stress (e.g. non purposeful movements, facial expression of fear). The original RDOS has recently been adapted to critically ill patients (IC-RDOS) [7, 14] and to mechanically ventilated patients (MV-RDOS) [15-17].

However, the MV-RDOS has not yet been studied in noncommunicative patients, and its responsiveness to relieving interventions is not known. We conducted the present study to fill

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this gap and test the following hypotheses. First, we hypothesized that MV-RDOS would correlate with dyspnea intensity in communicative patients. Second, we hypothesized that MV-RDOS would bear a relationship with biomarkers that have previously been shown to vary with dyspnea intensity, such as the electromyographic activity of inspiratory muscles (e.g. parasternal intercostals and alae nasi) [18, 20, 21] or electroencephalographic signatures of respiratory-related cortical activation (such as pre-inspiratory potentials) [17, 22, 23]. We predicted that this relationship would be similar in communicative and noncommunicative patients. Third, we hypothesized that MV-RDOS would respond to relieving interventions (ventilator settings adjustments [2, 18] and administration of morphine [19]) in both categories of patients, and that this response would parallel that of dyspnea in communicative ones.

Patients and methods

This study was conducted prospectively in a 10-bed ICU of a 1,600-bed university hospital, over a one-year period (clinical trial registration number NCT02801838). The study protocol was approved by the appropriate legal and ethical authorities (ID-RCB: A01743-46). Informed consent was obtained from patients or their next of kin.

Patients

Intubated or tracheostomized patients were eligible for inclusion in the study: (1) when they had been intubated and mechanically ventilated for at least 24 hours, (2) when all respiratory cycles were triggered by the patient with pressure support mode, (3) in the case of communicative patients, when a positive answer was provided to two of the following questions: “is your breathing uncomfortable,” “are you bothered by your breathing,” “is your breathing difficult” and either a respiratory rate > 25 breaths/min or visible inspiratory contractions of neck muscles were observed, (4) in the case of noncommunicative patients, when a MV-RDOS score of ≥ 2.6 was calculated [15] and either a respiratory rate > 25

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breaths/min or visible inspiratory contractions of neck muscles were observed [17] and (5) when the physician in charge was planning therapeutic relieving interventions. Relief was considered achieved when criteria 3) or 4) were no longer present [17]. Patients were considered noncommunicative if one of the following three criteria were not met: 1) RASS between -2 and +2, 2) absence of delirium according to the Confusion Assessment Method for the ICU (CAM-ICU) and 3) ability to consistently self-report dyspnea, attested by a D-VAS variation not exceeding 10 mm for three consecutive measures [2, 7].

Exclusion criteria were intense agitation defined by RASS > +2 likely to compromise the quality of the recordings, age < 18 years, and pregnancy.

Measurements and data processing

Respiratory measurements and breathing pattern. Differential pressure sensor (Validyne, Northridge, USA) for airway pressure assessment, pneumotachograph (Flow Sensor, Hamilton Medical AG, Rhazuns, Switzerland) for flow assessment, and infrared capnometer (MicroStream®, Medtronic, Dublin, Ireland) for end-tidal partial pressure of carbon dioxide ($EtCO_2$) assessment were connected one after the other between the endotracheal tube and the Y piece of the ventilator circuit. For each condition, mean Tidal volume (V_T) inspiratory time (T_I), respiratory rate and $EtCO_2$ were calculated over a 10-minute period (**Figure E1**).

Detection and quantification of patient-ventilator asynchronies. We calculated the ineffective triggering index (ITI) and the double triggering index (DTI) in each condition, as previously performed [24, 25] (**Text E1**).

Dyspnea. A 100-mm D-VAS was used to assess self-reported dyspnea only in communicative patients. The MV-RDOS (**Table 1, Figure E2**) [17] was calculated in both communicative and noncommunicative patients, using a specifically developed smartphone application (DOS-calc). The D-VAS and MV-RDOS were assessed by three medical research staff (M.D., C.B., S.C).

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Electromyogram of extra-diaphragmatic inspiratory muscles. Alae nasi and parasternal intercostal EMG signals were collected using surface electrodes (Kendall/Arbo, Medtronic, Dublin, Ireland) [18, 21, 22]. Raw EMG signals were band-pass filtered (50-400 Hz), root-mean-squared (EMG-RMS) and smoothed over 1-second fixed windows (Labchart 7, ADInstruments, Dunedin, New Zealand) [18, 21, 22]. The area under the curve (AUC) of the envelope (EMGauc) was divided into inspiratory time-locked epochs and averaged over a 10-minute period (**Figure E3**).

Electroencephalogram recordings and processing. Electroencephalographic recordings were performed to look for signatures of respiratory-related cortical activation, as previously described [17, 23, 26]. This is presented in detail in the electronic supplement (Text E2). Two approaches were used. Firstly, a matrix covariance analysis was conducted on continuous EEG recordings to detect connectivity changes between a "baseline" condition, a "ventilator settings adjustment" condition and a "morphine" condition (Riemannian analysis). With this approach, receiver operating characteristic curves (ROCs) are constructed to evaluate the performances of the classifiers that discriminate between the experimental conditions in terms of prediction area under the curve (AUC). An AUC of 1 indicate perfect discrimination, an AUC of 0.5 indicate random discrimination, and an AUC of 0.7 or more is considered satisfactory [17]. Secondly, to correlate these electrical state/connectivity changes with respiratory suffering/activity, EEG segments time-locked on inspiration were averaged to detect a pre-inspiratory activity at the vertex. This is indicative of a cortical contribution to the inspiratory effort [17, 23], considered to originate in the supplementary motor area [17, 23]. A pre-inspiratory potential (PIP) is considered present if the slope of the averaged EEG signal departs from zero between 0.5 and 1.5 seconds before inspiration (Figure E4).

Study protocol

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An initial recording was performed immediately after inclusion and was defined as the "Baseline" condition. A first therapeutic intervention, consisting of adjustments of ventilator settings ("Adjustments trial"), was performed. Ventilator adjustments were applied to at least one setting among pressure support level [18, 27, 28], cycling-off [25] inspiratory trigger [24], PEEP [29] or inspired oxygen fraction (FiO_2), left to the discretion of the physician in charge of the patient. More details on our local guidelines for ventilator settings adjustment are available in **Table E1**. A second recording was then performed. After this first intervention, if the inclusion criteria previously defined in each subgroup were still met, a second intervention, consisting of opioid administration, was initiated ("Morphine trial"). Repeated intravenous bolus injections of 2 mg morphine hydrochloride were administered every 3 minutes until disappearance of the criteria, or until a maximum cumulative dose of 10 mg was reached. A third recording was then performed. These therapeutic interventions were initiated after the exclusion of any other cause of dyspnea that could be rapidly treated (e.g. airway obstruction, pneumothorax, severe acidosis or fever). Each trial consisted of a 10-minute recording stored on a computer for further analysis. At the end of each trial, dyspnea intensity was rated using a D-VAS in communicative patients, and the MV-RDOS was calculated in all patients.

Statistical analysis

Statistical analysis was performed with Prism 6.01 (GraphPad Software, San Diego, CA) and Matlab software (MATLAB Version: 9.6.0.1174912 [R2019a]). Continuous variables are expressed as median and interquartile range and categorical variables are expressed as absolute and relative frequency. Continuous variables were compared between conditions by a Wilcoxon test. As patients in whom dyspnea resolved after adjustment of ventilator settings did not receive opioids, the numbers of patients were different between the last two conditions, precluding the use of Friedman's test. Categorical variables were compared using McNemar's test for paired data, as appropriate. The relationship between either D-VAS or MV-RDOS and

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EMG activity was modeled by mixed affine models with a fixed slope and a random intercept modeling a random patient effect, and their parameters were estimated with the maximum likelihood method. The correlation coefficient between either D-VAS or MV-RDOS and EMG activity was derived from Spearman correlation coefficient (Rho) and Nakagawa's coefficient of correlation R for mixed models, accounting for the repeated measures [30-32]. More precisely, whereas the marginal coefficient of correlation (R_M) only takes the variance explained by the fixed effect into account, the conditional coefficient of correlation (R_C) is the percentage of variance explained by both fixed and random effects. We therefore reported the Rho and the R_C in this manuscript. As the analytical confidence intervals for R_C were not available, the numerical value of R_C was estimated using the bootstrap method with the appropriate procedure to draw bootstrap samples (10,000 in this study) for the linear mixed model with repeated measures. The best MV-RDOS and EMG threshold value to predict D-VAS > 3 (clinically important dyspnea) [33], was tested in the communicative patients by generating the receiver operating curves (ROC) and best likelihood ratio. We calculated that to observe a 35% MV-RDOS reduction after therapeutic interventions [13, 15] in a repeated measures design with an alpha risk of 5% and an 80% power, the inclusion of at least 46 patients was needed. Given the risk of technical issues (EMG, EEG), we planned to include 50 patients. Details on the correlation analysis from mixed models are provided in **Table E2**.

Results

Study population characteristics

Fifty patients (only one tracheostomized) were included, 25 were communicative and 25 were noncommunicative (**Figure 1**) due to recently interrupted sedation or delirium (n=15), language barrier (n=5), ongoing sedation (n=3), hearing impairment (n=1) and

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misunderstanding of instructions (n=1). The main patients characteristics are provided in Table 2.

Therapeutic interventions, breathing pattern and patient-ventilator asynchronies

Changes in ventilator settings comprised an increase of pressure support level for 50 (100%) patients (from 7 [6-8] cmH_2O at "Baseline" to 15 [14-16] cmH_2O after "Adjustments trial", p<0.001) and a decrease of the cycling-off for 27 (54%) patients (from 30 [25-30]% at "Baseline" to 25 [15-25]% after "Adjustments trial", p<0.001). Ventilator setting adjustments did not significantly differ between communicative and noncommunicative patients (**Table E3** and **E4**). Relief was incomplete after "Adjustments trial" in 25 (50%) patients which consequently received 10 [9–10] mg of morphine hydrochloride (**Figure 1**). The maximum dose of 10 mg was reached in 19 (76%) of these patients.

The impact of therapeutic interventions on breathing pattern is described in **Table 3**.

The ineffective triggering index did not vary between "Baseline" (0.0 [0.0–0.1] %) and "Adjustments" (0.1 [0.0–0.7], p=0.836) or "Morphine trials". The double triggering index significantly decreased between baseline (0.0 [0.0–0.5]) and "Morphine trial" (0.0 [0.0–0.0], p=0.027) (**Table E5**)."

Dyspnea and MV-RDOS

In communicative and noncommunicative patients, "Adjustments trial" were associated with a decrease in MV-RDOS, which further decreased after "Morphine trial" (**Figure 2**). The impact of therapeutic interventions on each item of the MV-RDOS is reported in **Table 4**. Compared to "Baseline" (60 [39 – 70] mm), D-VAS decreased after "Adjustments trial" (34 [20 – 52] mm, p<0.001) and further decreased after "Morphine trial" (19 [6 – 40] mm, p=0.002). Figure 3 shows the correlation between D-VAS and MV-RDOS (Panel A) and the D-VAS individual response after therapeutic interventions (Panel B). Two patients had an

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increase in D-VAS after ventilator settings adjustments. Individual MV-RDOS responses to treatment are represented in the **Figure E5**.

A MV-RDOS of 3.0 predicted a D-VAS > 3 with 70% sensitivity and a 77% specificity, with an AUC under the ROC of 0.78 (95% confidence interval [CI] 0.66–0.90, p<0.001). The AUC under the ROC was 0.75 (95%CI 0.62–0.88, p=0.001) for the EMGauc of the alae nasi muscle and 0.66 (95%CI 0.51–0.82, p=0.047) for the EMGauc of the parasternal intercostal muscle.

Electromyographic activity of parasternal intercostal muscles and alae nasi muscles

The EMGauc of parasternal intercostal muscles and alae nasi muscles at baseline and following therapeutic interventions is shown in **Figure 2** (lower panels). Individual EMGauc responses to treatment are represented in the **figure E6**.

In communicative and noncommunicative patients, “Adjustments trial” decreased the EMGauc of the parasternal intercostal and alae nasi muscles, which further decreased after “Morphine trial”. A significant positive correlation was observed between MV-RDOS and EMGauc for both alae nasi and parasternal intercostal muscles (**Figure 4**).

Respiratory-related cortical activity changes

Electroencephalogram was successfully recorded and could be analyzed in 43 patients.

Influence of dyspnea-oriented interventions on cortical activity. The AUC of the Riemannian classifier was 0.76 (95%CI 0.65–0.86, p<0.001) to discriminate "Baseline” vs. “Adjustments trial” indicating that modifying ventilator settings was associated with changes in cortical connectivity.

The proportion of patients exhibiting PIP was significantly higher during "Baseline" than during "Adjustments" (17/43 [40%] vs. 9/43 [21%], McNemar's test p=0.039, **Figure E7**), suggesting a respiratory contribution to the connectivity changes. Connectivity changes were

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also observed between "Baseline" and "Morphine" (AUC 0.82, 95%CI 0.65–0.98, p<0.001) and between "Adjustments" and "Morphine" (AUC 0.74, 95%CI 0.57–0.93, p<0.001), but without significant changes in PIP occurrences.

Relationship between cortical activity, dyspnea and MV-RDOS. In the 25 communicative patients, D-VAS was higher in the patients in whom a PIP was identified than in the other patients (62 [31–76] mm vs. 34 [18–55] mm, p=0.047). In the whole population, MV-RDOS was higher in patients in whom a PIP was identified than in the other patients (4.9 [4.2–6.3] vs. 4.0 [2.1–4.9], p=0.002).

Discussion

In line with our working hypotheses, this study suggests that MV-RDOS could provide clinicians with an operational surrogate of dyspnea in noncommunicative intubated patients. Firstly, MV-RDOS was correlated with D-VAS in the communicative patients, to which the noncommunicative patients were very similar (same characteristics -**Table 2**-, same ventilator adjustments -**Tables E3** and **E4**-, similar responses to therapeutic interventions -**Table 3**-). Secondly, MV-RDOS was correlated with inspiratory muscle EMG activities in the two subpopulations, in a manner similar to the D-VAS-EMG correlation observed in communicative patients. MV-RDOS was higher in patients in whom a PIP was identified than their counterparts. Thirdly, MV-RDOS scores decreased significantly in response to therapeutic interventions otherwise known to alleviate dyspnea, namely ventilator setting adjustments [2, 22, 32] and morphine administration [1]. These findings are reminiscent of previous studies that validated the behavioral pain scale based on its response to pain-provoking [34] and pain-relieving interventions [35].

Comparison with existing data

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The MV-RDOS - DVAS correlation found here compares well with the IC-RDOS correlation reported by Persichini et al [7]. In the present study, a MV-RDOS of 3 was the best predictor to infer a D-VAS > 3, slightly higher than in the MV-RDOS development study [15, 16]. The MV-RDOS - EMG correlations observed in our patients constitute a novel information. It is interesting to note the similarity between this correlation and the D-VAS - EMG correlation found in our communicative patients and reported by Schmidt et al. in similar circumstances [18]. If one accepts that these data support the value of inspiratory EMG as dyspnea surrogate, then the above similarity lends value to MV-RDOS as such a surrogate. In response to ventilator settings adjustments, D-VAS decreased by 43% in our communicative patients, which is consistent with the results reported by Schmidt et al. in a similar clinical setting [2]. Regarding the EEG signatures of respiratory-related cortical activation, our data extend the pioneer observations of Raux et al. who reported also a 50% reduction in the occurrence of pre-inspiratory potentials and a 0.89 (95%CI 0.58–0.84) prediction AUC regarding connectivity changes after ventilator setting adjustments [17]. Our study is seemingly the first to describe the MV-RDOS response to ventilator settings adjustments. MV-RDOS decreased by 32% and 28% in noncommunicative and communicative patients, respectively ($p = 0.342$). Taking into account the D-VAS - EMG correlation, the magnitude of the MV-RDOS changes is similar to the magnitude of the D-VAS changes. In this regard, it is interesting to note that a 10-15% decrease in D-VAS is generally accepted as a clinically important difference [37]. Our study is also seemingly the first to describe the response of both D-VAS and MV-RDOS to morphine in mechanically ventilated patients. The 44% D-VAS reduction observed in our communicative patients is consistent with the dyspnea relief obtained by opioids in terminally ill patients. [36]. The 38% MV-RDOS reduction in our noncommunicative patients is consistent with the 34% RDOS reduction following opioids administration observed in a palliative care setting by Campbell et al. [13].

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Physiological considerations

Dyspnea bears a close relationship with the neural drive to breathe [39-43], as illustrated in our patients by the D-VAS-EMG correlation, by the parallel effects of relieving interventions on D-VAS, respiratory rate and EMG activity, and by brain cortical activity changes. Our study shows that MV-RDOS also bears a close relationship with the neural drive to breathe. Indeed, we found a significant MV-RDOS-EMG correlation and observed that treatment-associated MV-RDOS decrease was partly driven by changes in the "neck inspiratory muscles" and the " paradoxical breathing" items of the scale. These observations cohere with the known recruitment of extra-diaphragmatic inspiratory muscles in response to acute inspiratory loading, [40] and the relationship between this recruitment and dyspnea [18, 20]. Yet, treatment-associated MV-RDOS decrease was also driven by the disappearance of the facial expression of fear, suggesting a relationship between the neural drive to breathe and the affective reaction to breathing difficulties [44]. This formally validates MV-RDOS as a multidimensional measure. This could make MV-RDOS useful in communicative patients, as a complement to DVAS that must be obtained in them [45].

Limitations

Like the original RDOS, MV-RDOS is subject to some degree of operator-dependence, especially regarding facial expression of fear identification [7]. The detection of abdominal paradox requires training (**Figure E2**), and neck muscle contraction depends on patients' morphology (palpation may help reduce assessment errors). We did not evaluate within-observer and between-observer reliability, but we hypothesize that the overall good interobserver agreement described for IC-RDOS [7] should also apply to MV-RDOS. We acknowledge that the MV-RDOS has so far been tested in only two small cohorts [15, 16] and

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that larger scale multicentric validation is necessary. We believe that the EMG - EEG - MV-RDOS relationships and the MV-RDOS treatment responsiveness observed in this study lend sufficient support to the validity of MV-DOS. In addition, a correlation between the surface EMG activity of inspiratory muscles and the MV-RDOS was expected since the MV-RDOS integrates clinical signs of neck muscles activations. Of note, like other RDOS scales, and like dyspnea assessment, MV-RDOS is a discontinuous measure that requires a patient-stakeholder interaction and takes some time to establish (about 1 minute in our experience). Finally, although our population size was determined according to an a priori calculation, we acknowledge that the population was small, and restricted by the need to respect inclusion criteria. This certainly limits the generalizability of the results.

Clinical considerations and perspectives

In our patients, adjusting ventilator settings with a relieving objective resulted in an important increase in the pressure support level. Although this did not occur in our patients (in whom tidal volume remained below 8 ml/kg), such pressure support increases could lead to over-assistance and the associated risks of patient-ventilator asynchronies (ineffective triggering), ventilator induced diaphragm dysfunction and ventilator-induced lung injury [46, 47]. Clinicians caring for mechanically ventilated patients can therefore be confronted with the impossible choice of letting their patients experience respiratory suffering with possible long-term consequences [3, 48] or exposing them to dangerous side effects of mechanical ventilation. Our study shows that resorting to opioids could possibly provide a solution to this conundrum and paves the way for corresponding clinical trials.

The inability to communicate in no way excludes the possibility that an individual is experiencing respiratory suffering and needs appropriate respiratory suffering-relieving treatment. As observed with pain [49], it cannot be excluded that sedation in ICU patients may

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give a falsely reassuring external appearance of respiratory comfort. This could be mitigated by the fact that profoundly sedated patients (RASS -4 or -5) would probably not be able to accurately perceive respiratory suffering.

In conclusion, our study shows that MV-RDOS can contribute to identify respiratory suffering in mechanically ventilated patients and to evaluate the effects of relieving interventions. Despite the study limitations, we therefore believe that MV-RDOS can become a valuable tool for doctors and nurses to better help their mechanically ventilated patients achieve respiratory comfort in routine care. We also believe that MV-RDOS can become a useful outcome for interventional trials testing pharmacological or nonpharmacological interventions with this particular objective.

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Tables

Table 1. Calculation of the Mechanical Ventilation – Respiratory Distress Observation Scale (MV-RDOS) [15]

Variables	Score
0-	**3.3**
1- Heart Rate (bpm)	**+ (Heart rate)/65**
2- Use of neck muscles during inspiration	
if present	**+ 1**
if absent	**- 1**
3- Paradoxical breathing during inspiration	
if present	**+ 1**
if absent	**- 1**
4- Facial expression of fear	
if present	**+ 1**
if absent	**- 1**
5- Respiratory rate (cycles/min)	**+ (Respiratory rate)/50**

Numerical calculation of the MV-RDOS is performed by summing all items.

For better accuracy, heart and respiratory rate should be calculated over a 15 or 30 second period. When patient morphology did not allow clear visualization of the neck muscle, an excessive use of the neck muscle during inspiration could be assessed by direct palpation of the neck muscles (sternocleidomastoid or scalene muscles). The detection of the paradoxical motion of the abdomen during inspiration is depicted in the figure E2 in the online Supplement and is characterised by an abdomen that moves in during inspiration.

Table 2. Main patient characteristics

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Variables	Total n = 50	Communicative n = 25	Non-communicative n = 25	*P*
General characteristics at inclusion				
Gender (male), *n (%)*	37 (74)	18 (72)	19 (76)	*0.838*
Age, *years*	67 (61–76)	66 (63–77)	68 (60–73)	*0.794*
BMI, *kg/m²*	26.9 (23.9 – 31.7)	26.1 (22.9–27.7)	29.4 (25.5–32.4)	*0.024*
Length of stay, *days*	6 (3–10)	7 (4–11)	6 (4–11)	*0.688*
Duration of mechanical ventilation, *days*	9 (4–10) 8 (4–9)	6 (3–9)	6 (4–10)	*0.843*
Underlying chronic diseases				
Chronic respiratory disease, *n (%)*	21 (42)	10 (40)	11 (44)	*0.863*
Chronic heart failure, *n (%)*	4 (8)	1 (4)	3 (12)	*0.522*
Reason for mechanical ventilation				
De novo acute respiratory failure, *n (%)*	18 (36)	9 (36)	9 (36)	*1.000*
Acute-on-chronic respiratory failure, *n (%)*	11 (22)	7 (28)	4 (16)	*0.467*
Coma, *n (%)*	12 (24)	3 (12)	9 (36)	*0.047*
Extrapulmonary septic shock, *n (%)*	6 (12)	2 (8)	4 (16)	*0.667*
Others, *n (%)*	3 (6)	1 (4)	2 (8)	*0.486*
Severity scores				
SAPS II at admission	52 (35–62)	49 (32–58)	57 (36–65)	*0.125*
SOFA at inclusion	6 (3–9)	6 (3–8)	5 (4–9)	*0.927*
Physiological variables at inclusion				
Systolic BP, *mmHg*	142 (119–152)	142 (119–150)	135 (120–153)	*0.836*
Diastolic BP, *mmHg*	66 (58–72)	70 (59–74)	62 (57–72)	*0.177*
Heart rate, *bpm*	98 (87–112)	94 (87–114)	98 (87–111)	*0.908*
Respiratory rate*, cycles/min*	30 (25–35)	29 (23–34)	30 (25–38)	*0.228*
Pulse oximetry, %	96 (95–99)	97 (95–100)	95 (94–98)	*0.432*
RASS	0 (-1–1)	0 (0–0)	-1 (-3–1)	***0.025***

Continuous variables are expressed as median (interquartile range) and categorical data as number (%).
BMI, body mass index; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment; BP, blood pressure; RASS, Richmond analgesia and sedation scale.

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Table 3. Impact of therapeutic interventions on breathing pattern

Patients		Baseline N=50	Adjustments N=50	Morphine N=25
All patients n=50	Inspiratory time, *ms*	820 (633–957)	875 (761–1109)*	984 (807–1126)*§
	Tidal volume, *mL*	441 (367–540)	499 (416–626)*	512 (447–611)*§
	Tidal volume, *mL/kg*	6.4 (5.6–8.1)	7.7 (6.3–9.4)*	8.4 (7.1–10.0) *§
	Respiratory rate, *cycles/min*	28 (23–34)	25 (20–31)*	21 (17–25)*§
	Peak pressure, cmH_2O	13.8 (12.2–16.5)	22.1 (18.7–25.4)*	23.2 (20.6–26.2)*
	End-tidal CO_2, *mmHg*	33.2 (28.8–37.3)	32.0 (27.0–36.0)*	33.3 (30.2–38.3)§
	V_T/Ti, *l/sec*	0.56 (0.44–0.62)	0.56 (0.47–0.62)	0.52 [0.43-0.59]
	Ti/Ttot	0.36 (0.31–0.40)	0.39 (0.33–0.43)	0.35 (0.28–0.39)
Non-communicative n=25	Inspiratory time, *ms*	810 (610–927)	823 (730–1050)*	1046 (878–1187)*§
	Tidal volume, *mL*	401 (369–476)	494 (399–557)*	516 (468–626)*§
	Tidal volume, *mL/kg*	6.2 (5.5–7.4)	7.1 (5.8–9.0)*	8.4 (6.7–10.0)*§
	Respiratory rate, *cycles/min*	29 (24–34)	30 (22–34)	22 (17–26)*§
	Peak pressure, cmH_2O	13.8 (12.3–16.8)	21.9 (18.4–25.4)*	21.7 (20.3–26.1)*
	End-tidal CO_2, *mmHg*	33.2 (31.0–36.8)	31.7 (29.9–35.6)*	33.3 (30.8–36.5)§
Communicative n=25	Inspiratory time, *ms*	830 (644–1130)	939 (800–1200)*	940 (765–1114)*§
	Tidal volume, *mL*	472 (366–569)	550 (436–639)*	512 (437–607)*§
	Tidal volume, *mL/kg*	7.6 (5.7–8.3)	8.6 (7.1–9.9)*	7.6 (8.4–11.3)*§
	Respiratory rate, *cycles/min*	31 (27–39)	21 (20–29)*	19 (16–23)*§
	Peak pressure, cmH_2O	13.8 (12.0–16.4)	22.6 (20.0–24.6)*	23.9 (22.1–26.7)*
	End-tidal CO_2, *mmHg*	30.5 (27.8–38.0)	33.2 (26.3–36.0)*	34.4 (29.6–39.3)*§

Continuous variables are expressed as median (interquartile range). P values vs. Baseline for each intervention. The respiratory rate reported is the respiratory rate of the ventilator.

* P Value < 0.05 vs. Baseline. § P value < 0.05 vs. Adjustments trial

Baseline, at baseline before interventions; Adjustments, after ventilator setting adjustments;

Morphine, after injection of morphine

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Table 4. Impact of therapeutic interventions on each item of the Mechanical Ventilation-Respiratory Distress Observation Scale (MV-RDOS)

Patients	MV-RDOS variables	Baseline n=50	Adjustments n=50	Morphine n=25
All patients n=50	Heart rate, *bpm*	98 (87–112)	96 (83–110)	100 (79–107)
	Respiratory rate, *cycles/min*	28 (23–34)	25 (20–31)*	21 (17–25)*§
	Use of neck muscles, n (%)	43 (86)	29 (58)*	11 (44)*
	Paradoxical breathing, n (%)	10 (20)	2 (4)*	0 (0)*
	Facial expression of fear, n (%)	19 (38)	7 (14)*	1 (4)*
	MV-RDOS value	**5.5 [4.2–6.6]**	**4.2 [2.1–4.7]***	**2.5 [2.1–4.2]*§**
Non-communicative patients n=25	Heart rate, *bpm*	98 (87–111)	95 (86–109)	95 (77–107)
	Respiratory rate, *cycles/min*	29 (24–34)	29 (22–32)*	22 (17–26)*§
	Use of neck muscles, n (%)	22 (88)	17 (68)	8 (57)*
	Paradoxical breathing, n (%)	5 (20)	2 (8)	0 (0)*
	Facial expression of fear, n (%)	12 (48)	6 (24)	1 (7)*
	MV-RDOS value	**6.3 [4.6–6.6]**	**4.3 [2.6–5.9]***	**3.9 [2.1–4.4]*§**
Communicative patients n=25	Heart rate, *bpm*	94 (87–114)	101 (78–111)	100 (93–106)
	Respiratory rate, *cycles/min*	29 (23–34)	21 (18–28)*	21 (19–23)*
	Use of neck muscles, n (%)	21 (84)	12 (48)*	3 (27)*
	Paradoxical breathing, n (%)	5 (20)	0 (0)*	0 (0)
	Facial expression of fear, n (%)	7 (28)	1 (4)	0 (0)
	MV-RDOS value	**4.6 [4.2–6.3]**	**3.3 [2.0–4.6]**	**2.3 [2.1–3.4]*§**

Continuous variables are expressed as median (interquartile range) and categorical data as number (%).

The respiratory rate reported is the respiratory rate of the ventilator.

* $p < 0.05$ vs. Baseline. § $p < 0.05$ vs. Adjustments trial.

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Figure Legends

Figure 1. Study flow-chart

IMV, invasive mechanical ventilation; MV, mechanical ventilation: RASS, Richmond agitation and sedation scale; D-VAS, dyspnea visual analog scale; distress, respiratory distress as defined in Methods.

Figure 2. Mechanical Ventilation – Respiratory Distress Observation Scale (MV-RDOS, upper panels) and the area under curve of the surface electromyographic activity (EMGauc) of the alae nasi (middle panel) and parasternal (lower panel) muscles at baseline and after therapeutic interventions

Boxes represent the median with the first and third quartile and whiskers represent the 5th and 95th percentiles. Dots represent outliers.

* $p < 0.05$ vs. Baseline. § $p < 0.05$ vs. Adjustments trial.

Baseline, at baseline before interventions; Adjustments, after ventilator setting adjustments; Morphine, after injection of morphine.

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Figure 3. Correlations between self-reported dyspnea (D-VAS) and the Mechanical Ventilation - Respiratory Distress Observation Scale (MV-RDOS) using Spearman correlation coefficient (Rho) and conditional correlation coefficients (R_C) from mixed affine models (Panel A), and individual D-VAS responses to therapeutic interventions, in the 25 communicative patients

Rho and R_C are expressed with their 95% confidence intervals. Line in the Panel A is the regression line.

Figure 4. Correlations between the surface electromyographic activity (EMGauc) of the alae nasi (upper panel) and parasternal (lower panel) muscles and the Mechanical Ventilation - Respiratory Distress Observation Scale (MV-RDOS) using Spearman correlation coefficient (Rho) and conditional correlation coefficients for mixed affine models (R_C)

Rho and R_C are expressed with their 95% confidence intervals. Lines are regression lines.

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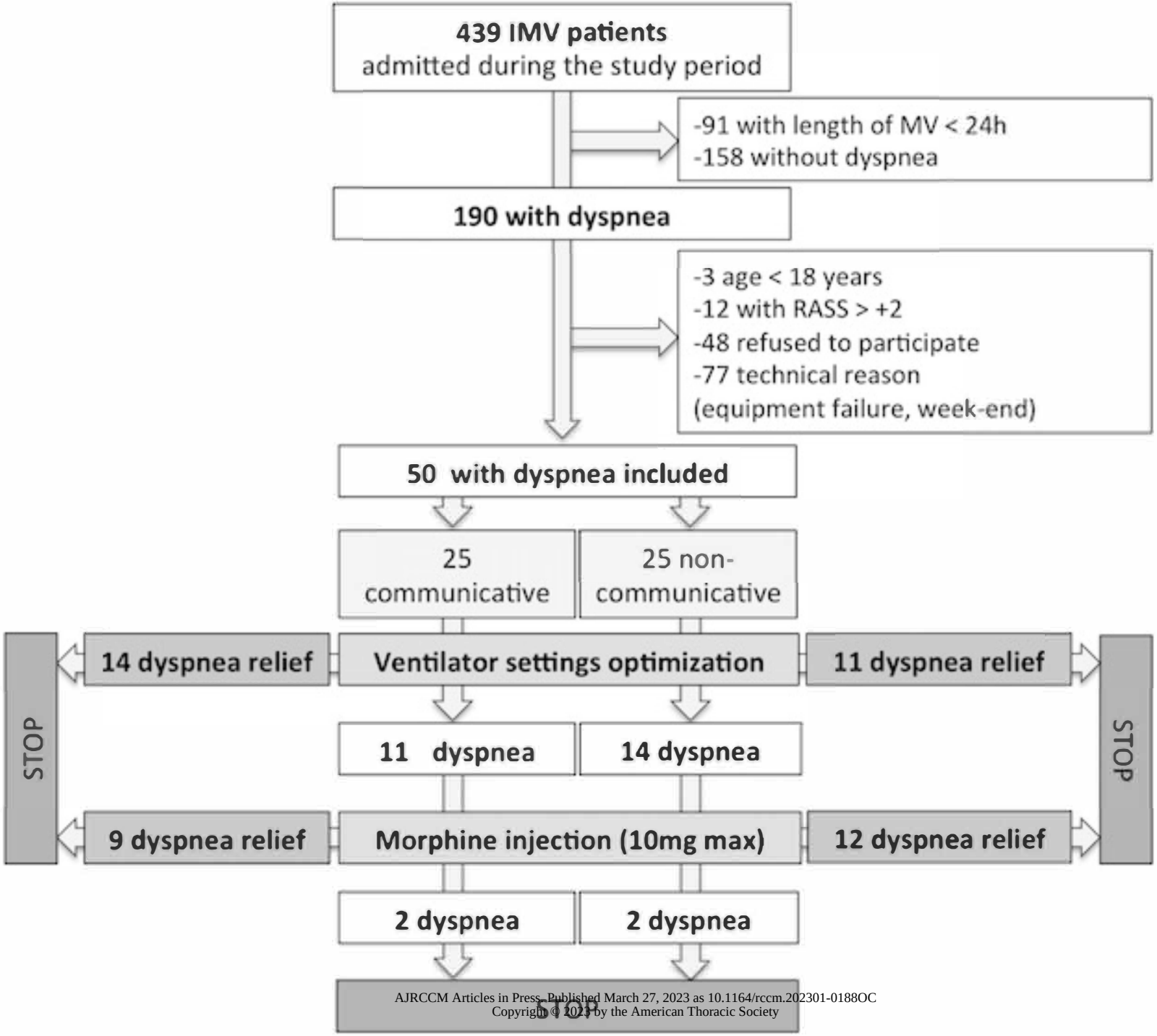

Figure 1

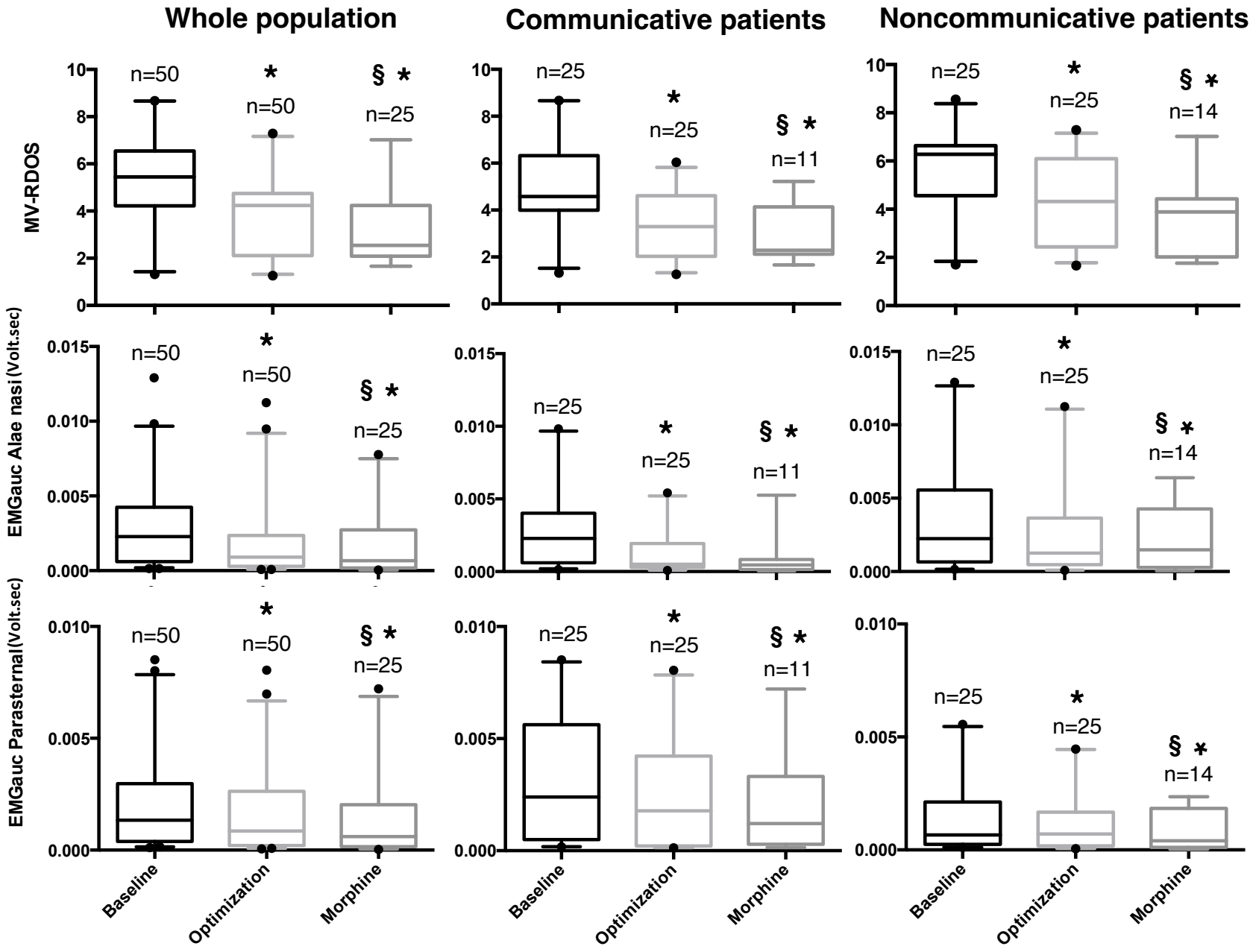

Figure 2

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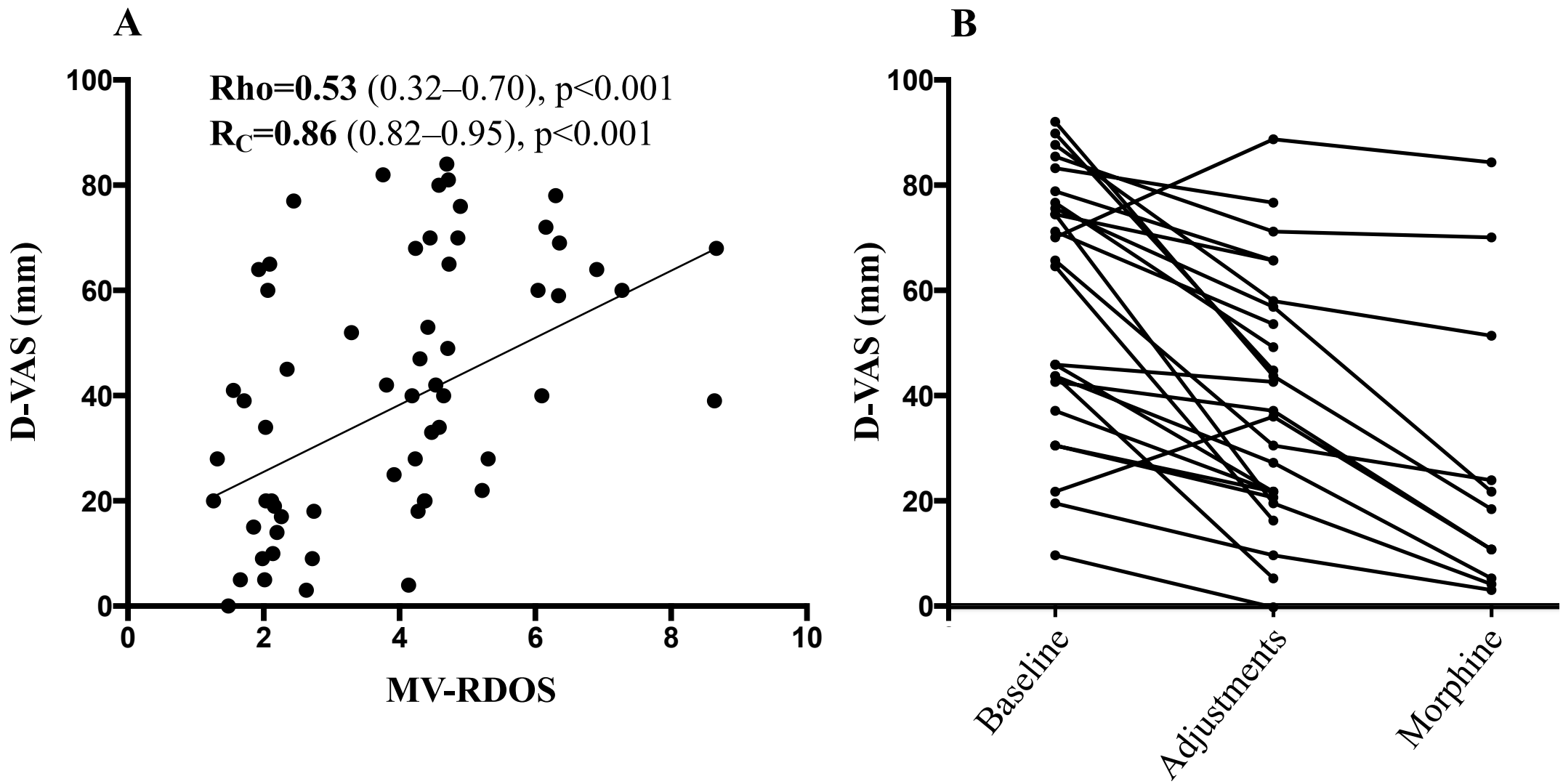

Figure 3

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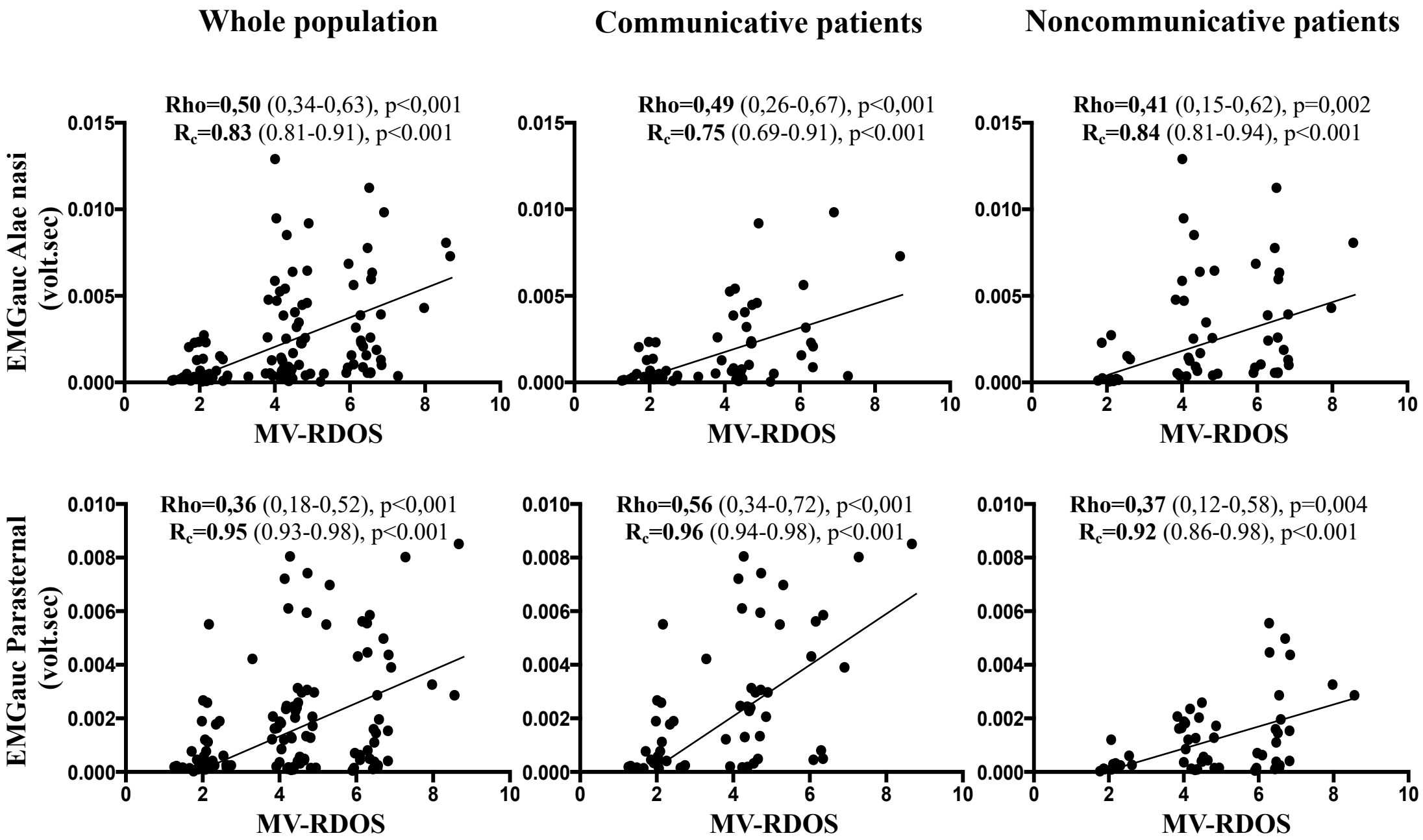

Figure 4

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Interventions relieving dyspnea in intubated patients show responsiveness of the Mechanical Ventilation – Respiratory Distress Observation Scale

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ONLINE DATA SUPPLEMENT

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Figure E7. Electroencephalographic recordings of a patient in whom the pre inspiratory potential (PIP) disappeared after ventilator settings adjustments

Text E1. Detection and quantification of patient-ventilator asynchronies

The two most frequently found asynchronies were quantified based on the flow and pressure recordings. Ineffective triggering was defined as an airway pressure drop > 0.5 cmH2O and a concomitant EMG activity not followed by a ventilatory cycle. Double triggering was defined as the presence of two ventilatory cycles and concomitant EMG activity separated by an expiratory time defined less than one-half of the mean inspiratory time, the first cycle being patient-triggered [24, 25]. We calculated the ineffective triggering index and the double triggering index, which are the total number of ineffective triggering or double triggering breaths divided by the total number of breaths (effectively and not effectively triggered).

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Text E2. Description of the electroencephalographic analyses

We used a 30 active scalp electrode system positioned according to the international EEG 10–20 system, referenced to FCz (ActiCap, Brain Products GmbH, Germany). Electrode impedances were kept below 5 kΩ. Signals were amplified and digitalized at a rate of 1000Hz using a BrainAmp amplifer (Brain Products, GmbH, Germany).

Pre-inspiratory potentials (PIP). The detailed PIP identification methodology has been described previously [1-9]. The PIP detection required EEG segmentation time-locked on inspiration and automatic marking of the start of inspiration was reported on the EEG raw signal (Fast Response Output 1.3 for Labchart 7 software). Selected EEG segments started 2000 ms before inspiration and ended 1000 ms after inspiration. The EEG signal was then divided into as many segments as inspiratory cycles (**Figure S4**). Segments with a signal gradient in excess of 5μV/ms or a maximal amplitude in excess of 50μV for 200ms or more were automatically rejected. The accepted segments were averaged, and a pre-inspiratory potential was suspected in the presence of a negative defection preceding inspiration in FCz. In such instances, a linear regression was fitted to the pre-inspiratory data range and a pre-inspiratory potential was considered present if the slope of the corresponding equation was positive and significantly different from zero.

Statistical distance between current EEG segment and reference period (classifier). The detailed Riemannian analysis methodology has been also described previously [6, 8, 10, 11]. we used an in-house developed and patented algorithm that classifies brain activity in different conditions using a semi-supervised approach. We tested for modified activity after adjustment of ventilator settings ("Adjustments trial") and Morphine administration ("Morphine trial") compared to reference activity before such interventions ("Baseline"). This involved a learning phase to define reference prototypes (first 20% of the "Baseline" period) followed by a detection phase to compare the covariance matrices from the "Adjustment trial" and the "Morphine trial" periods with the prototypes learned. To perform this analysis, EEG signals from frontal and central channels (F3, Fz, F4, C3, Cz, C4, FP1, FP2, F7, F8, FC3, FC4, FT7 and FT8) were segmented in 5-second sliding, 50% overlapped windows, down-sampled to 250Hz and band-pass filtered (8–24Hz) to enhance motor cortical activity (or mu rhythm [12]) found in this frequency band. Artefactual data windows were removed using an automated method that rejects outlier values on the basis of different statistics (amplitude, linear trend, joint probability and kurtosis [13, 14]). The criterion to reject contaminated epochs was based on z-scores, i.e the difference of a given statistic at a given epoch with respect to the mean across all epochs divided by their standard deviation. Once the reference period was characterized [6, 10] the statistical distance from the reference period was plotted as a function of time and compared for any given EEG segment with a rejection threshold beyond which the EEG covariance becomes statistically different from the reference situation. This is considered indicative of a significant change in brain activity. This threshold is obtained from the distribution of the distances between all the covariance matrices estimated from the reference period, where no significant changes are expected.

Performance of the classifier. The performance of the classifier was evaluated using a 10-fold cross-validation [10]. The reference period of the "Baseline" condition was divided into ten equal parts. Comparison between nine of these parts from the reference period and the data from the "Adjustments trial" and "Morphine trial" condition was repeated nine times to take into account

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all combinations. This allowed us to construct Receiver Operating Characteristic curves (ROCs) and calculate the corresponding areas under the curve (AUC) to summarize the sensitivity/specificity ratio of the classifier (one value for each patient; an AUC of 1 indicates perfect discrimination whereas an AUC of 0.5 indicates
random discrimination).

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Table E1. Local recommendations that guided physicians in the ventilator settings adjustments in pressure support mode.

Settings	
Pressure support [1-9]	Target a tidal volume of 8 ml/kg predicted body weight Never exceed a tidal volume 10 ml/kg predicted body weight
Expiratory trigger (cycling-off) [10-13]	Set up to a maximum 50 % of the peak inspiratory flow in chronic obstructive pulmonary disease (COPD) patients.

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	Set up to a minimum of 5% of the peak inspiratory flow in patients with pulmonary restrictive disease.
Inspiratory trigger [12, 13]	Set a flow trigger high sensitivity in COPD patients with ineffective triggering. Sensitivity should be reduced in case of autocycling.
Inspired oxygen fraction	Targeted to transcutaneous oxygen saturation ≥ 92%
Positive end expiratory pressure (PEEP) [4, 5, 14-17]	Do not exceed 12 cmH_2O Adjust to intrinsic PEEP in COPD patients

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Table E2. Correlation analyses for the mixed models

Predictor	**Response**	**R_M (95%CI)**	**R_C (95%CI)**	σ_f^2	σ_α^2	σ_ϵ^2	β_1 (95%CI)	$p_{\beta 1}$	p_α
MV-RDOS	EMGaucAN T	0.31 (0.20-0.47)	**0.83 (0.81-0.91)**	9.9	58.8	31.3	$5.9.10^{-4}$ (3.5-8.4)	<0.001	<0.001
MV-RDOS	EMGaucAN C	0.50 (0.26-0.66)	**0.75 (0.69-0.91)**	25.3	31.6	43.1	$6.3.10^{-4}$ (3.7-9.0)	<0.001	0.005
MV-RDOS	EMGaucAN NC	0.22 (0.12-0.40)	**0.84 (0.81-0.94)**	4.9	66.3	28.8	$5.3.10^{-4}$ (1.3	0.011	<0.001
MV-RDOS	EMGaucPara T	0.23	**0.95**	5.5	84.7	9.8	$2.6.10^{-4}$	<0.001	<0.001

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		(0.14-0.35)	**(0.93-0.98)**				(1.9-3.5)		
MV-RDOS	EMGaucPara C	0.24 (0.11-0.39)	**0.96 (0.94-0.98)**	5.5	86.6	7.9	$3.1.10^{-4}$ (1.7-4.4)	<0.001	<0.001
MV-RDOS	EMGaucPara NC	0.25 (0.10-0.47)	**0.92 (0.86-0.98)**	6.4	78.7	14.9	$2.4.10^{-4}$ (1.3-3.6)	<0.001	<0.001
MV-RDOS	D-VAS	0.54 (0.39-0.69)	**0.86 (0.82-0.95)**	29.6	44.1	26.3	7.6 (5.3-9.9)	<0.001	<0.001
D-VAS	EMGaucAN T	0.34 (0.18-0.55)	**0.69 (0.46-0.94)**	11.5	35.7	52.8	$3.0.10^{-5}$ (5.3-7.7)	0.009	<0.007
D-VAS	EMGaucPara T	0.25 (0.14-0.43)	**0.97 (0.95-0.99)**	6.3	87.6	6.1	$2.5.10^{-5}$ (1.4-3.7)	<0.001	<0.001

MV-RDOS, Mechanical Ventilation - Respiratory Distress Scale; EMGaucAN, surface electromyographic activity of the alae nasi muscles; EMGaucPara, surface electromyographic activity of the intercostal parasternal muscles; T, whole population (n=50); C, communicative patients (n=25); NC, noncommunicative patients (n=25); D-VAS, dyspnea visual analog scale, CI, confidence interval.

Terminology and explanations of the correlation analyses Table S2:

The linear mixed model is written as:

$y_{ij} = \beta_0 + \beta_1 x_{ij} + \alpha_i + \epsilon_{ij}\ with\ \alpha_i \sim N\left(0, \sigma_\alpha^2\right)\ and\ \epsilon_{ij} \sim N\left(0, \sigma_\epsilon^2\right)$

where y_{ij} is the jth observation of the ith subject, x_{ij} is the jth value of the fixed effect predictor for the ith subject, β_0 is the (grand) intercept, β_1 is the regression coefficient for the fixed effect predictor (slope), α_i is a zero mean subject-specific effect, assumed to be normally distributed with variance σ_α^2, and ε_{ij} is a zero mean residual, assumed to be normally distributed with variance σ_ε^2.

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σ_α^2 = var($\beta_1 x_{ij}$): variance explained by fixed effects,

σ_α^2: variance explained by random effects,

σ_ϵ^2: residual variance,

$R^2_M = \sigma_f^2 / (\sigma_f^2 + \sigma_\alpha^2 + \sigma_\epsilon^2)$, Nakagawa's marginal coefficient of determination, i.e. proportion of the total variance explained by the fixed effects

$R^2_C = (\sigma_f^2 + \sigma_\alpha^2) / (\sigma_f^2 + \sigma_\alpha^2 + \sigma_\epsilon^2)$, Nakagawa's conditional coefficient of determination, i.e. proportion of the variance explained by both fixed and random effects.

$R_{M =.} \sqrt{R2_M}$: marginal correlation coefficient

$R_C = \sqrt{R2_C}$: conditional correlation coefficient

$p_{\beta 1}$: p-value associated to the test of nullity of the slope β_1

p_α: p-value associated to the test of nullity of the variance of the random intercept σ_α^2

The observed difference between R_M and R_C therefore reflects the presence of a patient effect: while the slope of the relationship between MV-RDOS and muscle activity is the same for two different patients, they may have a different EMGauc parasternal value at baseline for a same MV-RDOS value, as EMG activities depend on each patient's morphology. As shown in Table S1, this is particularly true for the intercostal parasternal muscle surface EMGauc, which is more markedly influenced by the individual effect than the alae nasi muscles (lower R_M and greater R_C). In practical terms, this could be related to a greater between-individual variation in the thickness of the chest wall compared to that of the skin of the nose. This hypothesis is strongly supported by our data because we also found a strong negative correlation between body mass index and the parasternal EMGauc (Spearman coefficient correlation at baseline r=-0.51 95%CI -0.70 – - 0.25, p=0.003 and after ventilator setting adjustments r=-0.54 95%CI -0.75 – -0.28, p<0.001).

This is also true, to a lesser extent, for prediction of D-VAS by MV-RDOS **(Figure S2)**, because dyspnea is a complex, multidimensional sensation and the severity of dyspnea experienced by patients at baseline before any therapeutic intervention may vary between patients and two different patients with the same baseline MV-RDOS may report different levels (within a limited range) of dyspnea intensity.

We reported R_C in the manuscript because it reflects the strength of the correlation between MV-RDOS and EMGauc/D-VAS following therapeutic interventions for any patient, given the patient-dependent y-intercept. The high conditional coefficient R_C indicates a strong correlation, for any

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patient, between changes in the predictor (MV-RDOS) and changes in the response (EMGauc or D-VAS, for example).

Table E3. Ventilator setting modifications at Baseline and after ventilator settings adjustments (Adjustments)

Patients	Ventilator settings	Baseline (n=50)	Adjustments (n=50)	*P*
Whole population n=50	Pressure support, cmH_2O	7 (6–8)	15 (14–16)	*<0.001*
	PEEP, cmH_2O	5 (5–6)	5 (5–6)	*0.746*
	FiO_2, %	40 (30–40)	30 (30–40)	*0.898*
	Inspiratory trigger, *l/min*	1 (1–2)	1 (1–1)	*0.476*
	Expiratory trigger, *%*	30 (25–30)	25 (15–25)	*<0.001*

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Noncommunicative patients n=25	Pressure support, *cmH_2O*	7 (5–8)	14 (12–16)	*<0.001*
	PEEP, *cmH_2O*	5 (5–6)	5 (5–6)	*0.826*
	FiO_2, *%*	30 (30–40)	30 (30–40)	*0.898*
	Inspiratory trigger, *l/min*	2 (1–3)	1 (1–1)	*0.487*
	Expiratory trigger, *%*	30 (25–30)	25 (15–30)	*0.018*
Communicative patients n=25	Pressure support, *cmH_2O*	7 (6–8)	16 (14–16)	*<0.001*
	PEEP, *cmH_2O*	5 (5–6)	6 (5–6)	*0.724*
	FiO_2, *%*	40 (30–40)	40 (30–40)	*0.874*
	Inspiratory Trigger, *l/min*	1 (1–2)	1 (1–1)	*0.423*
	Expiratory trigger, *%*	30 (25–30)	25 (15–25)	*0.002*

Continuous variables are expressed as median (interquartile range) and categorical data as number (%).
PEEP, positive end-expiratory pressure; FiO_2, fraction of inspired oxygen

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Table E4. Ventilator setting variations (expressed as percentage) among communicative and noncommunicative patients

Ventilator settings and Variations vs. Baseline	Communicative patients (n=25)	Noncommunicative patients (n=25)	*P*
Increase in pressure support			
Number of patients, n (%)	25 (100)	25 (100)	*1.000*
Median percentage increase, %	50 (50–61)	50 (43–58)	*0.730*
Positive end-expiratory pressure			
Increase*:*			
Number of patients, n (%)	2 (8)	0 (0)	*0.768*
Median percentage increase, %	33 (25–42)	0 (0–0)	*0.897*
Decrease*:*			
Number of patients, n (%)	1 (4)	0 (0)	*0.879*
Median percentage decrease, %	20 (20–20)	0 (0–0)	*0.768*
Oxygen inspired fraction			
Increase*:*			
Number of patients, n (%)	0 (0)	0 (0)	*1.000*
Decreased*:*			
Number of patients, n (%)	2 (8)	0 (0)	*0.470*
Median percentage of decrease, %	33 (33-33)	0 (0–0)	*0.333*
Inspiratory trigger sensitivity			
Increased*:*			
Number of patients, n (%)	9 (36)	8 (32)	*0.884*
Median percentage increase, %	200 (100–400)	180 (100–200)	*0.853*
Decreased*:*			
Number of patients, n (%)	2 (8)	1 (4)	*0.556*
Median percentage decrease, %	39 (34–44)	29 (29–29)	*0.879*
Expiratory trigger			
Increased*:*			
Number of patients, n (%)	1 (4)	1 (4)	*1.000*
Median percentage increase, %	60 (60–60)	20 (20–20)	*0.867*
Decrease*:*			
Number of patients, n (%)	13 (52)	12 (48)	*0.777*
Median percentage decrease, %	40 (33–60)	40 (33–60)	*0.956*

Continuous variables are expressed as median (interquartile range) and categorical data as number (%)

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Table E5. Patient-ventilator asynchronies between baseline and therapeutic interventions in the whole population

Asynchrony	Baseline	Adjustments	Morphine
Ineffective triggering index, *%*	0.0 (0.0–0.9)	0.1 (0.0–0.7)	0.0 (0.0–0.4)
P value vs. baseline	-	0.836	0.852
P value vs. adjustments	-	-	0.749
Double triggering index, %	0.0 (0.0–0.5)	0.0 (0.0–0.3)	0.0 (0.0–0.0)
P value vs. baseline		0.115	**0.027**
P value vs. adjustments			0.172

Ineffective triggering (IT) was defined as an airway pressure drop > 0.5 cmH_2O not followed by a ventilatory cycle. Double triggering (DT) was defined as the presence of two ventilatory cycles separated by a very short expiratory time defined as less than one-half of the mean inspiratory time, the first cycle being patient-triggered [25]. We calculated the ineffective triggering index and the double triggering index, which are the total number of IT, or DT breaths divided by the total number of breaths (effectively and not effectively triggered).

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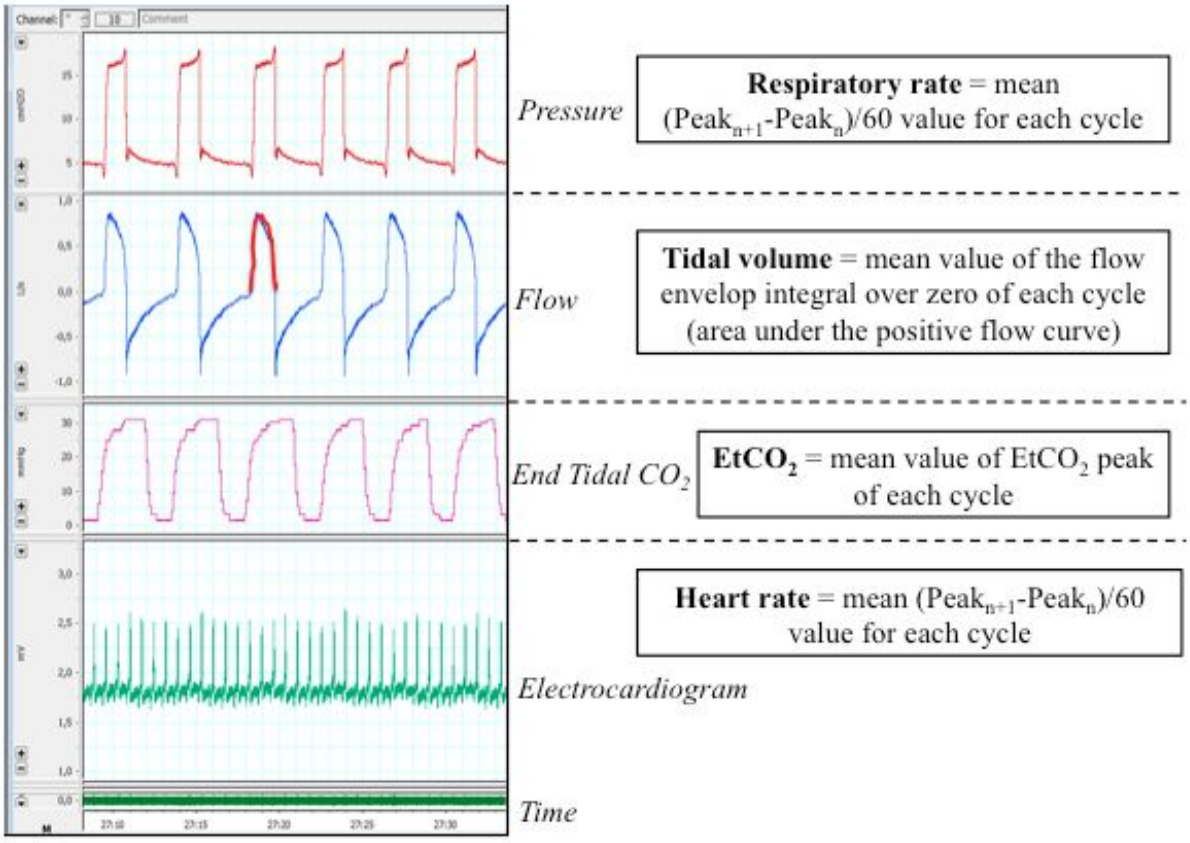
Figure E1. Processing of the pressure, flow, end tidal CO_2 ($EtCO_2$) and electrocardiogram signal



We analyzed around 300 cycles for each patient in each condition to calculate the mean respiratory rate, tidal volume, $EtCO_2$ and heart rate in each experimental condition.

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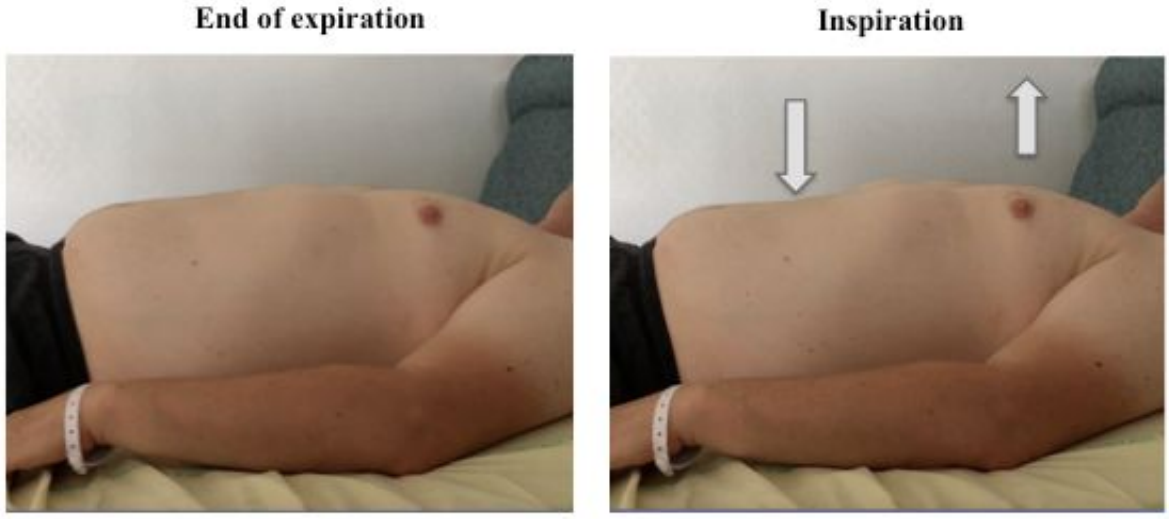
Figure E2. Detection of the paradoxical breathing during inspiration



Paradoxical breathing or paradoxical motion of the abdomen during inspiration traduces diaphragmatic weakness/failure and is defined as an inward move of the abdominal wall during inspiration. Generally, diaphragm weakness is compensated by an increase in the activity of extra-diaphragmatic inspiratory muscles, which causes an excessive expansion of the chest during inspiration, which reinforces the inward move of the abdomen.

To optimize the detection of a paradoxical motion of the abdomen during inspiration patients should be laid down or in a seated position with the chest inclined below 20°. In mechanically ventilated patients, the level of ventilatory assistance should be reduced as much as possible (if possible, disconnect the patients 5 seconds from the ventilator), to sensitize the observation of the abdomen paradoxical motion. One hand on the chest with the other hand on the abdomen may help to visualize ventilatory movements.

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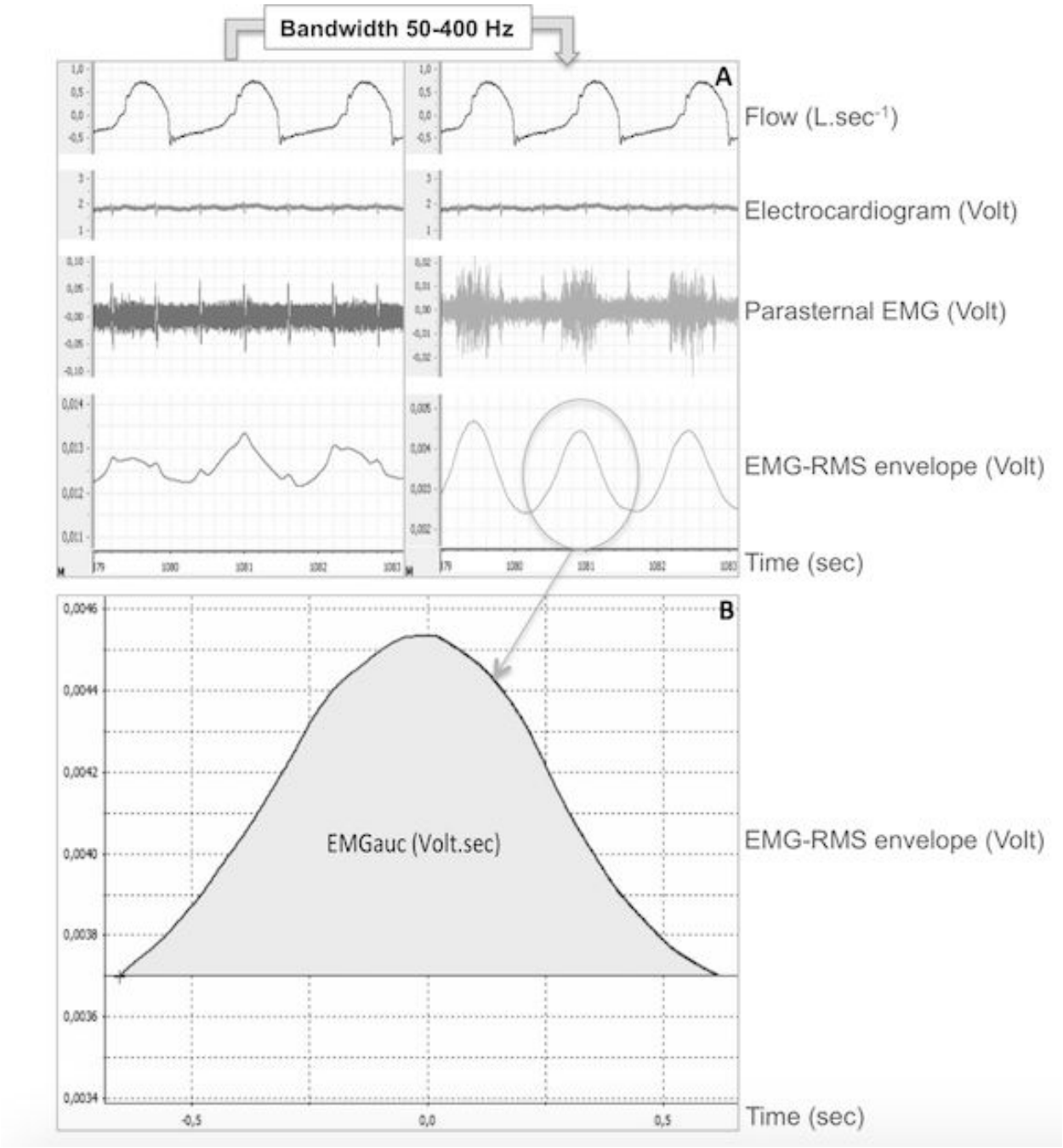
Figure E3. Processing of the parasternal electromyographic (EMG) signal [18, 27]



Panel A depicts a 4-second recording without (left) and with a 50-400 Hz bandwidth filter (right) leading to an optimized root-mean-squared electromyogram (EMG-RMS) envelope signal. Panel B depicts the parasternal area under curve of the RMS-EMG (EMGauc) time-locked on a respiratory cycle.

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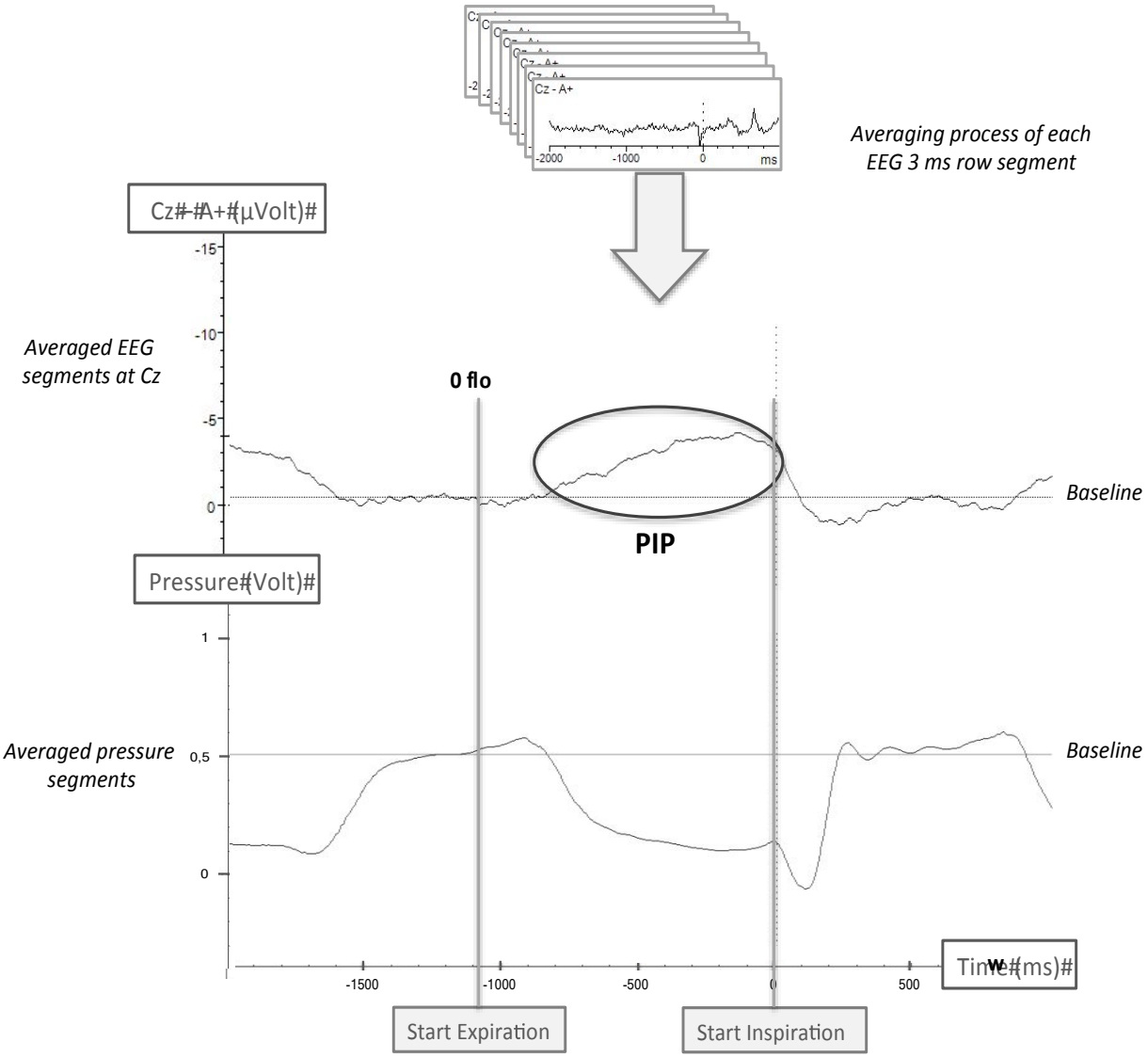
Figure E4. Identification of pre-inspiratory potential (PIP)



Each segments start 2000 ms before inspiration and ends 1000 ms after. This averaging process results to an averaged EEG (upper panel) and Pressure (lower panel) signals of 3000 ms. A pre-inspiratory potential was suspected in the presence of a negative defection preceding inspiration in FCz. In such instances, a linear regression was fitted to the pre-inspiratory data range and a pre-inspiratory potential was considered present if the slope of the corresponding equation was positive and significantly different from zero.

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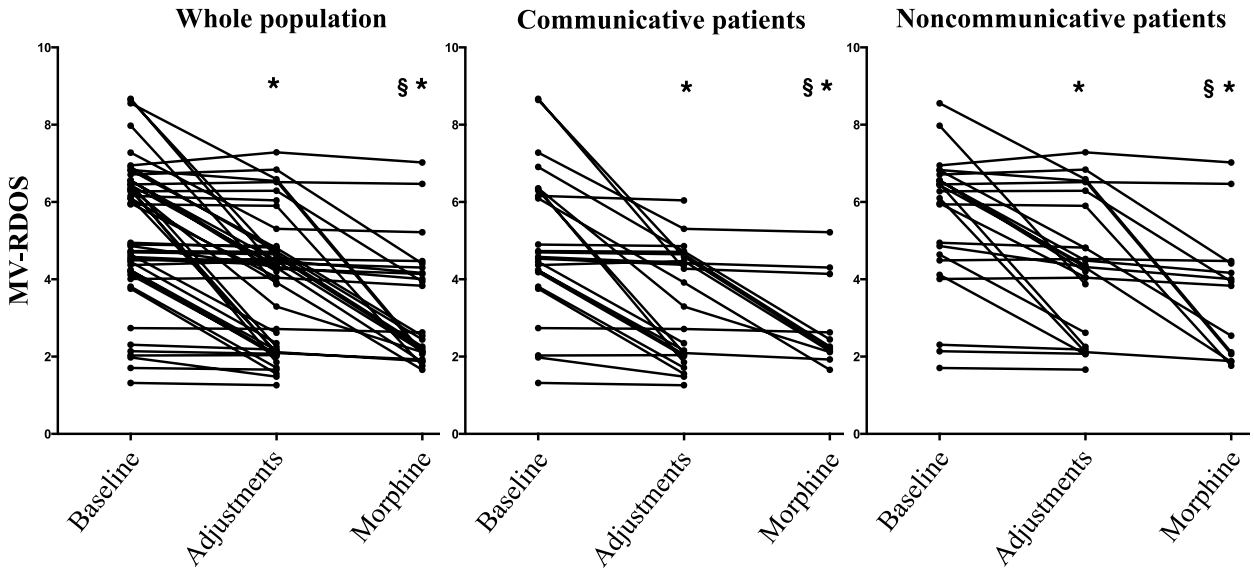
Figure E5. Individual mechanical ventilation – respiratory distress observation scale (MV-RDOS) responses to treatment in the three distinct populations



* $p < 0.05$ vs. Baseline. § $p < 0.05$ vs. Adjustments trial.

Baseline, at baseline before interventions; Adjustments, after ventilator setting adjustments; Morphine, after morphine administration.

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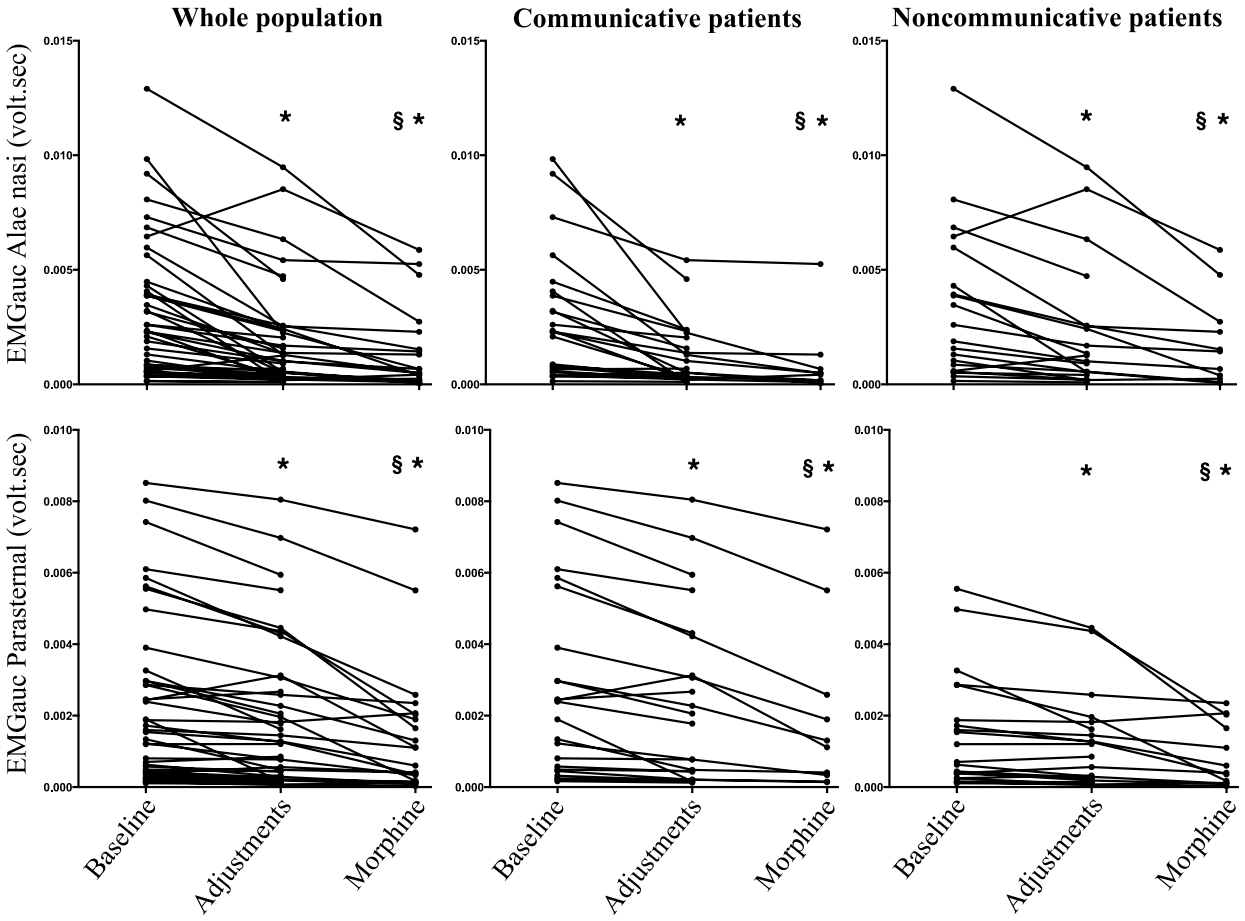
Figure E6. Individual responses of the surface electromyographic activity (EMGauc) of the alae nasi (upper panel) and parasternal (lower panel) to interventions in the three distinct populations



* $p < 0.05$ vs. Baseline. § $p < 0.05$ vs. Adjustments trial.

Baseline, at baseline before interventions; Adjustments, after ventilator setting adjustments; Morphine, after morphine administration.

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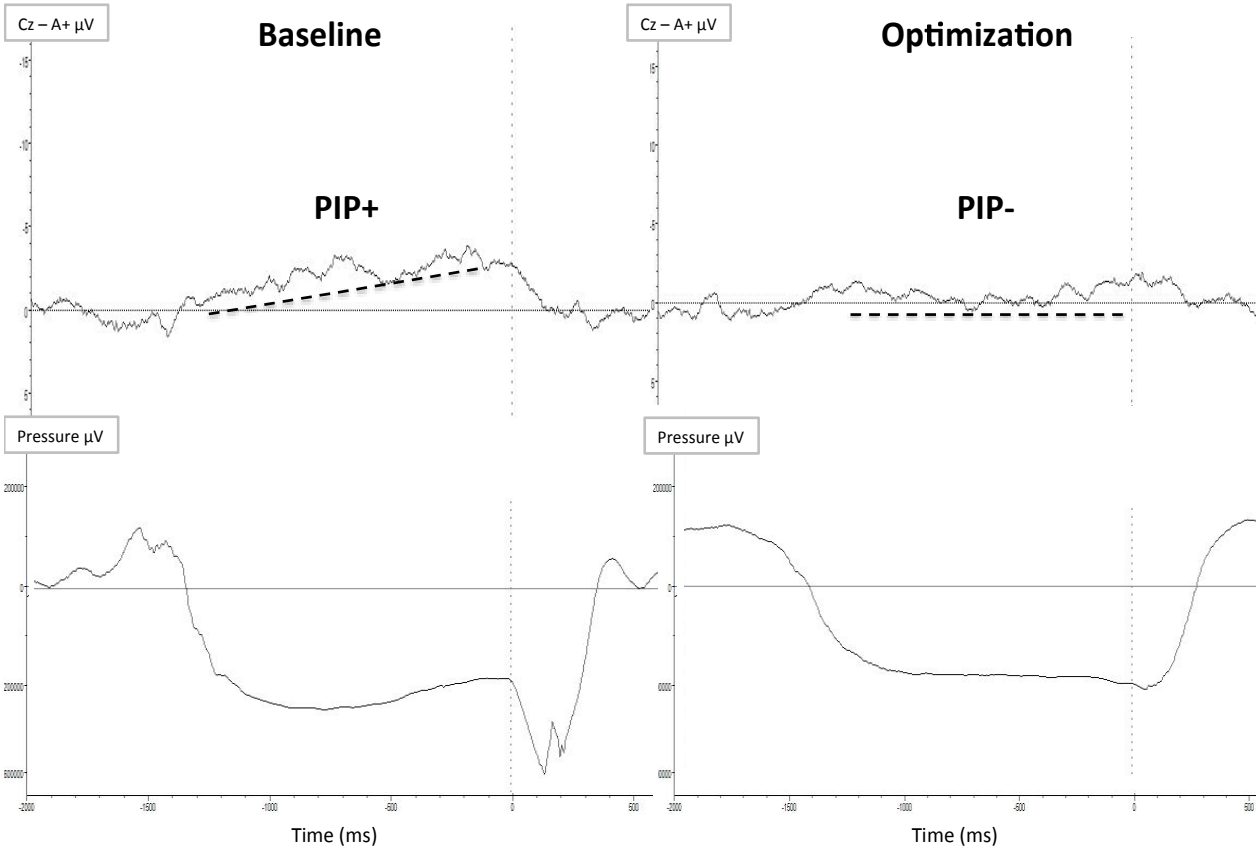
Figure E7. Electroencephalographic recordings of a patient in whom the pre inspiratory potential (PIP) disappeared after ventilator settings adjustments



Pre inspiratory potential before (left panel) and after optimization of ventilator settings (right panel) in patient n°25. Each trace is the average of 3-seconds recordings EEG (upper panels) or pressure (lower panels) recordings, time-locked on the beginning of the inspiration. As underscored by the dashed lines, we observed a negativation of the PPI after ventilator settings optimization.

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