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ABSTRACT

BACKGROUND: Swings of central venous pressure (ΔCVP) may reflect those of pleural and esophageal (ΔPES) pressure and, therefore, the strength of inspiration. Strong inspiratory efforts can produce some harm. Herein we preliminarily assessed the diagnostic accuracy of ΔCVP for strong inspiratory efforts in critically-ill subjects breathing spontaneously.

METHODS: We measured ΔCVP and ΔPES in 48 critically-ill subjects breathing spontaneously with zero end-expiratory pressure (ZEEP) or 10 cmH_2O of continuous positive airway pressure (CPAP). The overall diagnostic accuracy of ΔCVP for strong inspiratory efforts (arbitrarily defined as ΔPES >8 mmHg) was described as the area under the receiver operating characteristic (ROC) curve, with 0.50 indicating random guess. The agreement between ΔCVP and ΔPES was assessed with the Bland-Altman analysis.

RESULTS: ΔCVP recognized strong inspiratory efforts with an area under the ROC curve of 0.95 (95% confidence intervals, 0.85-0.99) with ZEEP and 0.89 (0.76-0.96) with CPAP, both significantly larger than 0.50 (p<0.001). With the best cut-off value around 8 mmHg, the diagnostic accuracy of ΔCVP was 0.92 (0.80-0.98) with ZEEP and 0.94 (0.83-0.99) with CPAP. With ZEEP, the median difference between ΔCVP and ΔPES (bias) was -0.2 mmHg, and the 95% limits of agreement (LoA) were -3.9 and +5.5 mmHg. With CPAP, bias was -0.1 mmHg, and 95%-LoA were -5.8 and +4.5 mmHg. In both cases, ΔCVP correlated with ΔPES (r_s 0.81 and 0.67; p<0.001 for both).

CONCLUSIONS: In critically-ill subjects breathing spontaneously, ΔCVP recognized strong inspiratory efforts with acceptable accuracy. Even so, it sometimes largely differed from ΔPES.

Keywords: dyspnea; respiratory insufficiency; central venous pressure; physical examination

Introduction

Critically-ill subjects often make vigorous inspiratory efforts because of anxiety and increased respiratory drive, respiratory system resistance or elastance.[1-3] If too strong and numerous, these efforts will produce some harm. Blood flow will be diverted from more vital organs towards respiratory muscles, whole-body oxygen consumption will increase, and diaphragm damage will occur.[4-6] The resulting large driving transpulmonary pressure and tidal volume will injure the lungs.[7-10] Right ventricular preload, transmural pulmonary vascular pressure, and left ventricular afterload all will increase; if left ventricular function is poor, pulmonary edema will develop.[11,12] Clinicians should then recognize and treat these abnormally strong inspiratory efforts.[13-15]

During spontaneous breathing, tidal excursions ("swings") of pleural pressure can be estimated as changes of esophageal pressure (ΔPES).[16] In healthy volunteers, ΔPES is few cmH$_2$O during quiet breathing but higher than 10-15 cmH$_2$O during exercise.[17,18] During assisted mechanical ventilation, peak pressure of the respiratory muscles (another marker of the strength of inspiration) of 5-10 cmH$_2$O has been proposed as a reasonable target.[14] In a series of subjects undergoing a spontaneous breathing trial, ΔPES remained around 8 (95% confidence intervals [CI], 1-12) cmH$_2$O in those who succeeded but progressively increased to 15 (11-19) cmH$_2$O in those who failed.[19] An inspiratory effort with ΔPES >10 cmH$_2$O (or >8 mmHg) might thus be considered abnormally strong, vigorous, or excessive. Even if esophageal pressure is the reference method for measuring inspiratory efforts, it is not routinely measured.

Critically-ill subjects frequently have an intrathoracic central venous catheter. Due to shared anatomical location, swings of central venous pressure (ΔCVP) may reflect those of pleural and esophageal pressure. Previous studies have compared ΔCVP and ΔPES during spontaneous breathing.[20-24] The *agreement* (i.e., similarity) was sometimes poor, but the *correlation* (i.e., relationship) was quite always positive and significant. Because of the above finding, the idea of estimating ΔPES from ΔCVP has been abandoned.

This study aimed to determine the diagnostic accuracy of ΔCVP for strong inspiratory efforts (those with ΔPES >8 mmHg) in subjects recovering from critical illness and breathing spontaneously, and reassess the agreement and correlation between ΔCVP and ΔPES. We hypothesized that large ΔCVP generally predicts vigorous inspiratory efforts, although ΔCVP and ΔPES may sometimes differ from each other.

Materials and Methods

This was a single-center prospective observational study performed in a mixed Intensive Care Unit (ICU). It was approved by the local Ethics Committee (Comitato Etico Milano Area B; approval number 1629). Informed consent was always obtained. The study started on 15/07/2015 and ended on 26/01/2018. As the two members of the research team in charge of patients' recruitment (J.C. and E.S.) were not available in the ICU from 11/10/2015 to 8/5/2017, no patient was enrolled during that period of time.

Subjects breathing spontaneously or undergoing weaning from non-invasive or invasive mechanical ventilation were included if they met all of the following criteria: (1) they had a central venous catheter in the superior vena cava (as verified with chest X-ray) and an esophageal balloon as part of their care; (2) they could sustain two 20-minute trials of spontaneous breathing with either zero end-expiratory pressure (ZEEP) or continuous positive airway pressure (CPAP) (10 cmH$_2$O) according to their attending physicians (who were critical care specialists); and (3) a member of the research team was available. Enrollment occurred at any time during ICU stay. Patients with arrythmia or receiving extracorporeal membrane oxygenation were excluded.

Subjects who entered the study underwent two 20-minute trials of spontaneous breathing with ZEEP or CPAP in random order, in a semirecumbent position (30-45°). At the end of each trial: (1) we recorded the physiological variables of interest, including respiratory rate, heart rate, mean arterial pressure, ΔCVP, and ΔPES. Sedation and anxiety were graded according to the Richmond Agitation-Sedation Scale;[25] (2) patients described their breathing discomfort using the modified Borg Dyspnea Scale;[26] and (3) attending physicians categorized inspiratory efforts as "normal" or "strong" and patients as "hypovolemic", "normovolemic" or "hypervolemic" based on clinical examination and vital signs, excluding ΔCVP and ΔPES. Performance of arterial and/or central venous blood gas analyses was encouraged but not mandatory. The trial could be terminated early in case of complications (for example, desaturation or hemodynamic instability).

Central venous and esophageal pressures were recorded at 100 Hz, displayed in mmHg, and analyzed on a standard multiparameter monitor (Xprezzon – Spacelab Healthcare, Snoqualmie, WA, USA). Central venous pressure was measured relative to atmospheric pressure, with a fluid-filled transducer leveled 5 cm below the sternal angle. Esophageal pressure was measured with a balloon (SmartCath – Avea SmartCath Carefusion, San Diego, CA, USA) placed 30-40 cm from the

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nares with visible cardiac artifacts and inspiratory negative swings. The balloon was inflated with 1.0-1.5 ml of air and connected to an air-filled transducer leveled as needed to display the whole pressure tracing on the monitor (i.e., if the nadir of the esophageal pressure was too negative, the transducer was lowered). In subjects connected to a ventilator, concordance between ΔPES and changes in the airway (and pleural) pressure was verified during inspiratory efforts against an occluded airway (Baydur test).[16] If discordance was larger than 20% (ΔPES/ΔPAW <80% or >120%), position and inflation of the esophageal balloon were adjusted. ΔCVP and ΔPES were measured as maximum inspiratory falls, or negative deflections, from end-expiratory levels (Supplementary Digital Material: Supplementary Digital Figure 1). Five consecutive breaths with no evidence of forced expiration or esophageal spasm were analyzed and averaged.

Statistical analysis

Data are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Variables of interest were compared between groups with the Student's *t*-test, the Mann-Whitney rank-sum test, and the Fisher exact test.

Our primary aim was to verify whether ΔCVP discriminates between normal (ΔPES ≤8 mmHg) and strong (ΔPES >8 mmHg) inspiratory efforts in critically-ill subjects breathing with ZEEP or CPAP with moderate accuracy (i.e., with an area under the ROC curve of 0.80, significantly larger than 0.50).[27] Our definition of normal and strong inspiratory efforts was arbitrary; it was based on premises reported above. Of note, in a recent study conducted in patients on helmet non-invasive ventilation, ΔPES was 5 (3-6) cmH$_2$O in those who succeeded and 11 (7-17) cmH$_2$O in those who did not, who finally required endotracheal intubation.[28]

The sample size of the study was planned as follows. Type I error rate was set at 0.05; the type II error rate was set at 0.10 (power 0.90). The allocation rate that is the proportion between subjects with normal or strong inspiratory efforts was unknown. We cautiously estimated it could have ranged between 0.25 and 0.75. For an allocation rate as low as 0.25 or as high as 0.75, the required sample size was 48 subjects. For any intermediate allocation rate, the required sample size was smaller than that. We then decided to enroll 48 subjects with ZEEP and 48 subjects with CPAP.

The overall diagnostic accuracy of ΔCVP was described as the area under the ROC curve with Clopper-Pearson exact 95%-CI. The value with the highest sensitivity and specificity (Youden's

index) was considered the best cut-off point. Sensitivity, specificity, and diagnostic accuracy of ΔCVP had this point been used as the diagnostic criterion are reported with Clopper-Pearson exact 95%-CI.

Our secondary aim was to study the agreement and correlation between ΔCVP and ΔPES. Agreement was assessed with the Bland-Altman analysis and described as the median difference (bias) and 2.5[th] and 97.5[th] percentiles (95%-limits of agreement [LoA]).[29] We considered a divergence >20% (ΔCVP/ΔPES <80% or >120%) clinically unacceptable, as in the Baydur test.[16] Correlation was expressed as Spearman's rank coefficient (r_s).

Statistical analyses were run with MedCalc 19.0 (MedCalc Software, Ostend, Belgium) and SigmaPlot 11.0 (Jandel Scientific, San Jose, California). A p-value <0.05 was considered statistically significant.

Results

We enrolled 49 subjects in total. Forty-seven completed the two trials of spontaneous breathing with ZEEP and CPAP. One could be safely evaluated with CPAP but not with ZEEP, because of progressive desaturation. We thus ended up with 48 subjects evaluated with CPAP but 47 with ZEEP. One other subject was studied with ZEEP only, to reach the planned sample size in that group.

Thirty-three (67%) subjects were males and 16 (33%) females; the mean age was 60±15 years. The most common reason for admission to the ICU was acute respiratory failure due to pneumonia (18 [37%] subjects) or that developed after surgery (15 [31%] subjects). Only three (6%) subjects presented with acute heart failure. Other reasons for admission and initial severity of disease are reported in the Supplementary Digital Material (Supplementary Table 1).

The study was performed 5 [1-12] days after ICU admission. The main characteristics of the study population at that time are reported in Table 1. On average, ΔPES was 6.7 [4.6-9.8] (range 2.2-20.8) mmHg during spontaneous breathing with ZEEP and 6.1 [3.8-8.1] (range 2.0-19.2) mmHg with CPAP. Inspiratory efforts with ΔPES >8 mmHg were noted in 20 (42%) subjects with ZEEP and 12 (25%) subjects with CPAP.

In Table 2, we compare respiratory rate, heart rate, mean arterial pressure, results of arterial and central venous blood gas analyses (available for approximately three-quarters of the patients), level of sedation and anxiety (judged by the attending physicians) and breathing discomfort (referred by patients) between subjects with ΔPES ≤8 mmHg or >8 mmHg, during spontaneous breathing with ZEEP or CPAP. None of these variables consistently and significantly differed between the two groups. Moreover, none of these variables was significantly associated with the actual level of ΔPES (Supplementary Digital Material: Supplementary Digital Figure 2 and Figure 3). As for the attending physicians, they described as "normal" most of the inspiratory efforts with ΔPES >8 mmHg: 11 out of 20 (55%) with ZEEP and 10 out of 12 (83%) with CPAP (Table 2, Figure 1 and Supplementary Digital Figure 4, in the Supplementary Digital Material).

Diagnostic accuracy of ΔCVP

With ZEEP, ΔCVP discriminated inspiratory efforts with ΔPES ≤8 mmHg from those with ΔPES >8 mmHg with an area under the ROC curve of 0.95 (0.85-0.99) (p<0.001). With a best cut-off

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value of 8.2 mmHg, sensitivity was 0.85 (0.62-0.97), specificity 0.96 (0.82-1.00) and diagnostic accuracy 0.92 (0.80-0.98) (Figure 3). Positive and negative likelihood ratios were 23.8 (3.4-164.5) and 0.16 (0.05-0.40); positive and negative predictive values 0.94 (0.71-0.99) and 0.90 (0.76-0.96). With CPAP, the area under the ROC curve was 0.89 (0.76-0.96) (p<0.001). With a best cut-off value of 8.0 mmHg, sensitivity was 0.83 (0.52-0.98), specificity 0.97 (0.86-1.00) and diagnostic accuracy 0.94 (0.83-0.99) (Figure 2). Positive and negative likelihood ratios were 30.0 (4.3-210.7) and 0.17 (0.05-0.61); positive and negative predictive values 0.91 (0.59-0.99) and 0.95 (0.83-0.98).

Agreement and correlation between ΔCVP and ΔPES

With ZEEP, bias was -0.2 mmHg and 95%-LoA were -3.9 and +5.5 mmHg (Figure 3). Despite being significantly correlated (r_s 0.81; p<0.001), ΔCVP and ΔPES diverged by more than 20% in 16 (33%) subjects. With CPAP, bias was -0.1 mmHg and 95%-LoA were -5.8 and +4.5 mmHg (Figure 3). Once again, ΔCVP and ΔPES were significantly correlated (r_s 0.67; p<0.001) but differed by more than 20% in as many as 21 (43%) subjects. At the time of the study, four subjects had signs of hypervolemia and 44 had not. The frequency of divergent readings was 75% (3 subjects) in the former and 30% (13 subjects) in the latter, with ZEEP (p=0.101); 25% (1 subject) and 45% (20 subjects) with CPAP (p=0.629).

Additional results are reported in the Supplementary Digital Material (Supplementary Table 2-5).

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Discussion

In subjects recovering from critical illness and breathing spontaneously, ΔCVP discriminated normal (ΔPES ≤8 mmHg) from vigorous (ΔPES >8 mmHg) inspiratory efforts with moderate accuracy and better than any other recorded variable. With ZEEP or CPAP, the mean area under the ROC curve was 0.95 or 0.89, and the proportion of correct diagnosis, based on the best cut-off value around 8 mmHg (or 10 cmH$_2$O), was 0.92 or 0.94 respectively. Even so, ΔCVP was not reliable to estimate the exact value of ΔPES.

In line with previous studies,[20-24] we report a poor agreement but a positive and significant correlation between ΔCVP and ΔPES. In other words, even if ΔCVP and ΔPES were not always the same, smaller or larger ΔCVP generally reflected smaller or larger ΔPES. In order to clarify this issue, let us consider two patients, one with ΔCVP 1 mmHg and ΔPES 6 mmHg and the other one with ΔCVP 19 mmHg and ΔPES 11 mmHg. In both cases, there is no concordance between ΔCVP and ΔPES. However, as long as one considers ΔCVP and ΔPES similarly low or similarly high, based on a common threshold of 8 mmHg, ΔCVP will correctly signal a normal effort in the first patient and a vigorous effort in the second patient. Obviously, due to the lack of optimal agreement, ΔCVP will be inaccurate in some cases.

A recent audit conducted in 50 Countries has shown that one-third of patients in ICU with acute respiratory distress syndrome have some degree of spontaneous breathing. Even so, esophageal pressure is rarely measured.[30] Physiological variables cannot be accurately estimated based on clinical judgment alone, especially in critically-ill subjects. If their knowledge is meant to affect the process of care, they should be measured.[31,32] In this present work, attending physicians regarded as normal most of the inspiratory efforts with ΔPES >8 mmHg. Our decision to classify those efforts as vigorous or excessive was based only on physiological and pathological premises as more convincing data, from adequately designed clinical studies, were not available at the time of study design. Therefore, the threshold of ΔPES above which inspiratory efforts become injurious may differ from 8 mmHg. Moreover, our "black or white" approach, with inspiratory efforts classified as "normal" or "strong", is undoubtedly an oversimplification. The risk of lung injury probably progressively increases when ΔPES (and transpulmonary pressure) exceeds a critical, physiological value. A "grey-zone" approach may be more indicated.[33] Even so, we believe that the lack of a strong association between clinical judgment and ΔPES is much more important than suggesting a threshold for harm. Some inspiratory efforts were regarded as normal even if they were associated

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with ΔPES as large as 12-15 mmHg or even larger (as shown in Figure 1). A clinical diagnosis of respiratory distress is usually based on the presence of tachypnea, tachycardia, and hypoxia.[34,35] In our study population, respiratory rate, heart rate, and arterial oxygenation were not associated with the strength of inspiration. This was true for other possible signs of increased work of breathing, such as anxiety and central venous oxygen desaturation. In line with these findings, other authors have noted that respiratory rate and oxygenation do not reflect ΔPES in hypoxemic subjects treated in ICU.[28]

ΔCVP sometimes largely differed from ΔPES. Some discrepancy might be attributed to methodological issues. For example, we did not verify the exact position of the tip of the central venous catheter, immediately above the junction between the superior vena cava and the right atrium, with the electrocardiogram-technique;[36] and we did not remove cardiac artifacts from CVP and PES tracings.[37,38] We prioritized simplicity over more accurate, but also more complex, off-line analysis. Possible additional explanations include fluid overload or severe heart dysfunction with an exaggerated pressure-raising effect of increased venous return during inspiration;[39,40] use of a non-calibrated esophageal balloon in subjects disconnected from the ventilator (inaccurate measurement of ΔPES); uneven transmission of pleural pressure into the thorax.[10] The contribution of some of these factors was investigated as reported in the Supplementary Digital Material (Supplementary Table 2 and Figure 4). A large divergence between ΔCVP and ΔPES was not associated with higher end-expiratory CVP, a clinical diagnosis of hypervolemia, or the use of a non-calibrated esophageal balloon. Other variables that were not recorded probably had a role.

Some of the limitations of this study deserve a final comment. Our study population usually had an initial diagnosis other than heart failure and, by the time of enrollment, had grossly normal hemodynamics with no clear evidence of hypervolemia. In a non-compliant heart, the transmission of pleural pressure to the cardiac cavities can be blunted, and even small changes in volume can produce large changes in pressure: the agreement between ΔCVP and ΔPES will be particularly poor.[39,40] But even there, large ΔCVP will signal large (or even larger) falls in intra-thoracic pressure. Second, we did not study patients with early and severe acute respiratory distress syndrome, who frequently suffer from right heart failure (a relevant issue for reasons described above) and for whom strong inspiratory efforts are a major concern.[9] It is our opinion that in these patients, spontaneous breathing should be avoided unless the strength of inspiration can be measured with an esophageal balloon. Third, we did not compare ΔCVP with other markers of

respiratory effort, such as the electrical activity or the thickening fraction of the diaphragm.[41] We simply aimed to verify whether ΔCVP can be of any help to the attending physician. ΔCVP can be readily measured in all subjects with an intrathoracic central venous catheter, with no need for additional competencies. By measuring it, one may easily estimate the strength of inspiration in critically-ill patients, including those undergoing non-invasive ventilation or with a contra-indication to the positioning of an esophageal balloon (such as those with facial trauma or after esophageal surgery).

Conclusions

In this study population, ΔCVP discriminated inspiratory efforts with ΔPES ≤8 mmHg from those with ΔPES >8 mmHg with at least moderate accuracy and better than any other recorded variable. Even so, ΔCVP did not usually reflect the exact value of ΔPES.

WHAT IS KNOWN

- Clinicians should recognize and treat vigorous and potentially harmful inspiratory efforts that are commonly made by critically-ill patients.

- Even if swings in esophageal pressure (ΔPES) accurately reflect the strength of inspiration, they are not routinely measured.

WHAT IS NEW

- In critically-ill subjects breathing spontaneously, ΔPES cannot be estimated based on other physiological variables, including respiratory rate, heart rate, and hypoxia.

- Clinicians commonly regard as "normal" the inspiratory efforts associated with abnormally large ΔPES.

- Swing in central venous pressure (ΔCVP) can help clinicians discriminate between inspiratory efforts associated with smaller or larger ΔPES.

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NOTES

Conflicts of interest. The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions. Jacopo Colombo conceived and designed the study, collected data and wrote the manuscript. Elena Spinelli collected data and wrote the manuscript. Giacomo Grasselli enrolled participants and wrote the manuscript. Antonio Pesenti contributed to the design and the implementation of the project and wrote the manuscript. Alessandro Protti conceived and designed the study, performed the analysis, and wrote the manuscript. All authors read and approved this final version of the manuscript.

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Table 1. Main characteristics of the study population at study entry.

Airway	
• Endotracheal tube, n/total	7/49
• Tracheal cannula, n	16/49
• Natural, n	26/49
Ventilation	
• Assisted invasive ventilation, n	15/49
• Non-invasive ventilation, n	19/49
• Spontaneous breathing, n	15/49
FiO_2, %	40 [30-50]
Arterial pH	7.43±0.05
Arterial CO_2 tension, mmHg	41±5
Arterial O_2 tension, mmHg	91±24
Arterial O_2 saturation, %	95±2
$PaO_2:FiO_2$ (mmHg)	233±97
Heart rate, bpm	86±15
Mean arterial pressure, mmHg	86±13
Central venous pressure, mmHg	8±4
Central venous O_2 saturation, %	68±7
Lactate, mmol/l	1.1 [0.7-1.7]
Urinary output, ml/h	75 [57-102]
On vasopressor(s), n	1/49
On continuous renal replacement therapy, n	5/49
Clinical evaluation	
• Hypovolemic, n	9/49
• Normovolemic, n	36/49
• Hypervolemic, n	4/49

These are the main characteristics of the 49 subjects included in this study, at the time of their enrollment. FiO_2: fraction of inspiratory oxygen; PaO_2: arterial oxygen tension. Arterial blood gas analyses were not available for seven subjects; central venous O_2 saturation was not available for six subjects; arterial or central venous lactate was not available for three subjects; urinary output was not available for four subjects (those on continuous renal replacement therapy). Observed ICU-mortality was 8% (4 deaths).

Table 2. Comparison between subjects making inspiratory efforts with ΔPES ≤8 mmHg or >8 mmHg during spontaneous breathing with ZEEP or with CPAP.

	Spontaneus breathing with ZEEP			Spontaneous breathing with CPAP		
	ΔPES ≤8 mmHg	ΔPES >8 mmHg	p	ΔPES ≤8 mmHg	ΔPES >8 mmHg	p
n	28	20		36	12	
ΔPES, mmHg	4.9 [3.2-6.0]	11.4 [9.0-13.7]	NA	4.8 [3.5-6.5]	10.1 [9.8-15.0]	NA
Respiratory rate, bpm	22 [17-28]	23 [19-28]	0.515	20 [18-26]	19 [14-24]	0.141
Heart rate, bpm	85±13	90±14	0.195	86±14	87±15	0.740
Mean arterial pressure, mmHg	84±12	87±12	0.389	89±14	83±11	0.212
Arterial pH	7.45 [7.43-7.47]	7.42 [7.38-7.46]	0.120	7.43 [7.41-7.46]	7.43 [7.36-7.47]	0.278
Arterial CO_2 tension, mmHg	40±5	39±7	0.382	40±6	42±6	0.308
Arterial O_2 tension, mmHg	78 [66-95]	85 [68-143]	0.161	103 [87-134]	93 [67-115]	0.151
Arterial O_2 saturation, %	96 [91-98]	96 [93-99]	0.496	97 [96-99]	96 [93-98]	0.091
Central venous O_2 saturation, %	67±7	70±7	0.236	68±6	67±8	0.591
Blood lactate, mmol/l	1.6 [0.9-2.0]	1.0 [0.8-1.7]	0.289	1.5 [0.8-1.8]	1.1 [1.0-1.2]	0.152
ΔCVP, mmHg	5.5 [4.1-6.5]	10.5 [9.1-12.7]	<0.001	4.9 [4.2-6.2]	9.8 [8.3-13.2]	<0.001
Richmond Agitation-Sedation Scale	0 [0-0]	0 [0-0]	0.425	0 [0-0]	0 [-1-0]	0.658
Modified Borg Dyspnea Scale	1 [0-3]	2 [0-2]	0.682	0 [0-1]	0 [0-3]	0.460
Clinical evaluation						
• Normal effort, n	23	11	0.057	32	10	0.631
• Strong effort, n	5	9		4	2	

Herein we compare subjects with normal (swing of esophageal pressure [ΔPES] ≤8 mmHg) or strong (ΔPES >8 mmHg) inspiratory efforts during spontaneous breathing with zero end-expiratory pressure (ZEEP) or continuous positive airway pressure (CPAP) (10 cmH₂O). ΔCVP: swing of central venous pressure. The Richmond Agitation-Sedation Scale is a 10-point scale to describe individual sedation and anxiety where -5 denotes "unarousable", 0 denotes a calm and alert state, and +4 indicates "combative".[26] The modified Borg Dyspnea Scale is a 10-point scale to describe individual breathing discomfort where 0 means "none", and 10 means "maximal".[27] With ZEEP, arterial blood gas analysis was available for 35

subjects; arterial or central venous lactate for 41 subjects; arterial O_2 saturation for 37 subjects; central venous O_2 saturation for 35 subjects; and the modified Borg dyspnea scale for 45 subjects. With CPAP, arterial blood gas analysis was available for 37 subjects; arterial or central venous lactate for 41 subjects; arterial O_2 saturation for 38 subjects; central venous O_2 saturation for 36 subjects; and the modified Borg dyspnea scale for 45 subjects.

Figure 1. Relationship between the strength of inspiration as assessed by the attending physicians and actual ΔPES.

The attending physicians were asked to categorize the inspiratory efforts made by 48 critically-ill subjects breathing spontaneously with zero end-expiratory pressure (ZEEP) or continuous positive (10 cmH$_2$O) airway pressure (CPAP) as "normal" or "strong", based on their clinical assessment. They were not aware of the corresponding esophageal pressure (ΔPES) and central venous pressure (ΔCVP) swings. We report the ΔPES associated with those inspiratory efforts categorized as normal or strong (one dot per subject), with ZEEP or CPAP. With ZEEP, the inspiratory efforts categorized as normal were associated with a ΔPES of 5.9 [4.3-8.9] mmHg; those categorized as strong were associated with a ΔPES of 10.2 [6.0-15.5] mmHg (p=0.005 for comparison with normal ones). With CPAP, the inspiratory efforts categorized as normal were associated with a ΔPES of 6.1 [3.9-8.0] mmHg; those categorized as strong were associated with a ΔPES of 6.0 [3.2-12.6] mmHg (p=0.913).

Figure 2. Diagnostic accuracy of ΔCVP for strong inspiratory efforts.

We describe the overall diagnostic accuracy of swings of central venous pressure (ΔCVP) for inspiratory efforts with ΔPES ≤8 mmHg or >8 mmHg during spontaneous breathing with zero end-expiratory pressure (ZEEP) (panel A) or with continuous positive (10 cmH$_2$O) airway pressure (CPAP) (panel B). An area under the ROC curve (AUROC) of 1.0 indicates a perfect test (sensitivity and specificity both equal to 1.0), while a value of 0.5 indicates no diagnostic capability (random guess).

Figure 3. Agreement between ΔCVP and ΔPES during spontaneous breathing.

We describe the agreement between swings of central venous pressure (ΔCVP) and esophageal pressure (ΔPES) during spontaneous breathing with zero end-expiratory pressure (ZEEP) or with continuous positive (10 cmH$_2$O) airway pressure (CPAP). In panel A and C we report the Bland-Altman plot referred to spontaneous breathing with ZEEP (panel A) or CPAP (panel C). Solid line indicates bias that is the median difference between ΔCVP and ΔPES; dotted lines indicate 95%-limits of agreement. In panel B and D we describe the association between ΔCVP and ΔPES during

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spontaneous breathing with ZEEP (panel B) or CPAP (panel D). r_s: Spearman's rank correlation coefficient.
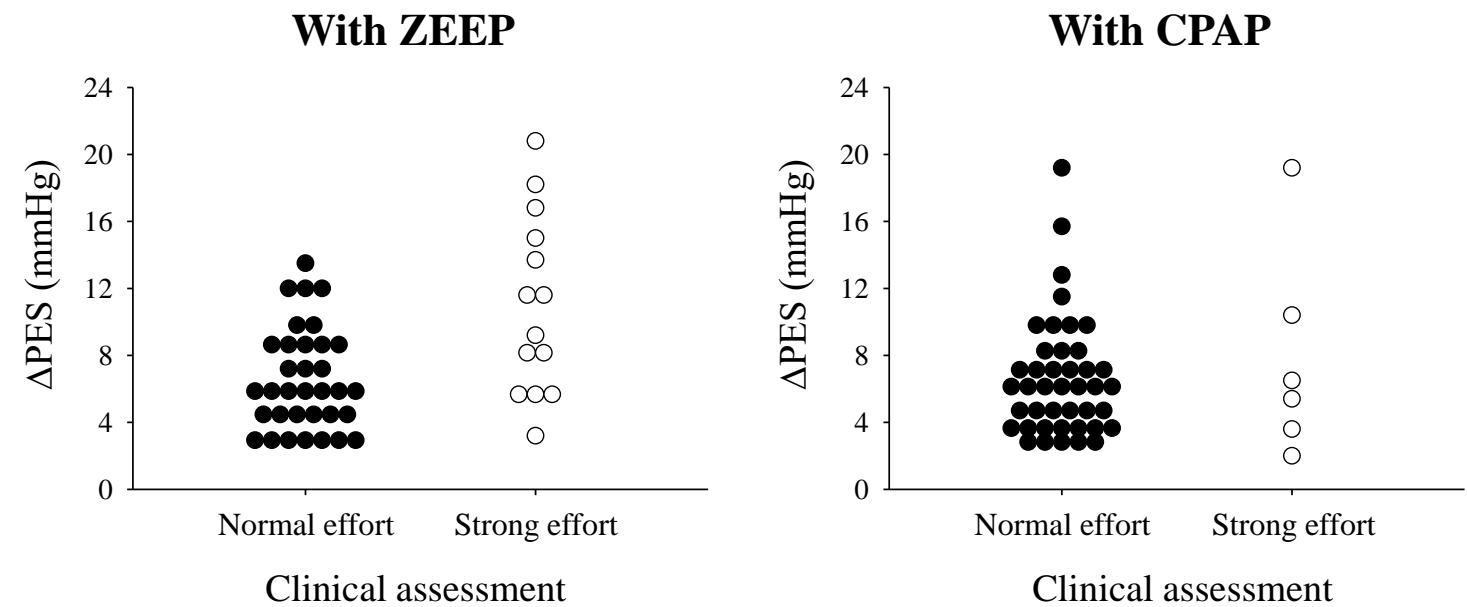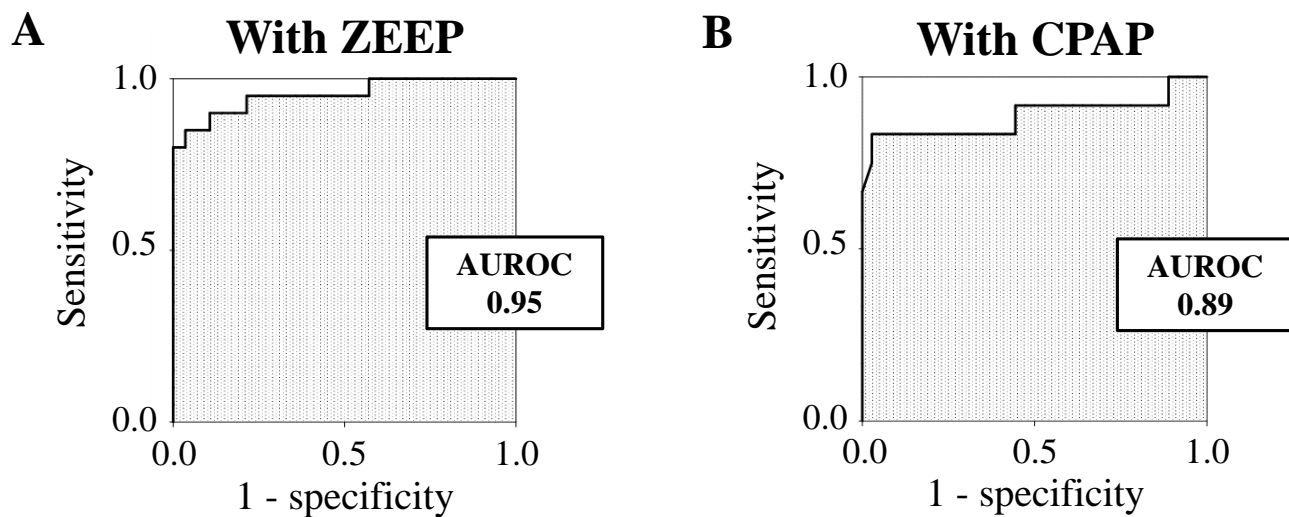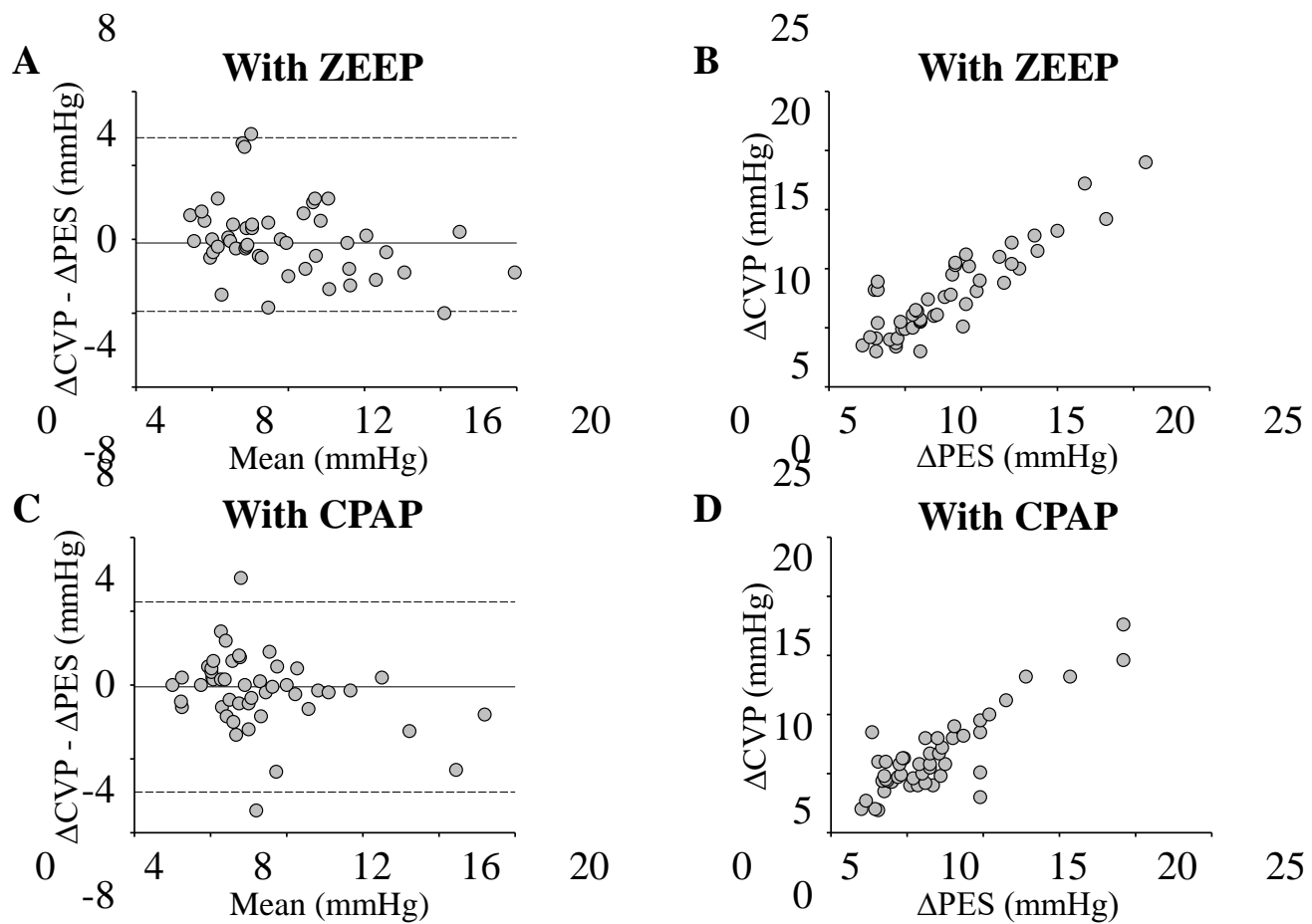
figure 1

Figure 2

Figure 3

Supplementary Digital Material

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