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An open-loop, physiological model based decision support system can reduce pressure support while acting to preserve respiratory muscle function

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ABSTRACT

Purpose: To assess whether a clinical decision support system (CDSS) suggests PS and FIO_2 maintaining appropriate breathing effort, and minimizing FIO_2.
Materials: Prospective, cross-over study in PS ventilated ICU patients. Over support (150% baseline) and under support (50% baseline) were applied by changing PS (15 patients) or PEEP (8 patients). CDSS advice was followed. Tension time index of inspiratory muscles (TTies), respiratory and metabolic variables were measured.
Results: PS over support (median 8.0 to 12.0 cmH_2O) reduced respiratory muscle activity (TTies 0.090 ± 0.028 to 0.049 ± 0.030; $p < .01$), and tended to increase tidal volume (VT: 8.6 ± 3.0 to 10.1 ± 2.9 ml/kg; $p = .08$). CDSS advice reduced PS (6.0 cmH_2O, $p = .005$), increased TTies (0.076 ± 0.038, $p < .01$), and tended to reduce VT (8.9 ± 2.4 ml/kg, $p = .08$). PS under support (12.0 to 4.0 cmH_2O) slightly increased respiratory muscle activity, (TTies to 0.120 ± 0.044; $p = .007$) with no significant CDSS advice. CDSS advice reduced FIO_2 by 12–14% ($p = .005$), resulting in median $SpO_2 = 96\%$ ($p < .02$). PEEP changes did not result in changes in physiological variables, or CDSS advice.
Conclusion: The CDSS advised on low values of PS often not prohibiting extubation, while acting to preserve respiratory muscle function and preventing passive lung inflation. CDSS advice minimized FIO_2 maintaining SpO_2 at safe and beneficial values.

1. Introduction

Management of mechanical ventilation can be considered a process of balancing competing goals. Inspired oxygen should be set to avoid hypoxaemia, without elevated values causing hyperoxaemia [1], and in patients with respiratory muscle activity and ventilated in pressure support (PS) mode, levels of PS should be selected which prevent excessive work of breathing while maintaining the strength of respiratory muscles [2]. Over-support, and minimal work of breathing (WOB) by the patient, may result in depression of respiratory drive and the development of ventilator induced diaphragmatic dysfunction (VIDD) [3]. Under support, and excessive patient WOB, may result in rapid shallow breathing [4], elevated muscle work and consequent muscle fatigue [5]. A complete understanding of the effects of changes in PS requires esophageal pressure (Peso) [5], which is not routinely measured.

Recently, a computerized clinical decision support system (CDSS), based on mathematical models of physiology, has been shown to provide appropriate advice on mechanical ventilation for a period of 4–8 h [6]. Changes in ventilator settings were evaluated from current clinical conditions, with physiological changes in PS evaluated using clinical variables.

This paper prospectively evaluates the ability of this CDSS to select appropriate ventilator settings in patients with spontaneous breathing activity following systematic over and under support. The ability of CDSS advice on PS to preserve respiratory muscle function is assessed from esophageal pressure measurements.

2. Materials and methods

2.1. Patients

Twenty-three patients were included from July 2015 to January 2017 at one university hospital general ICU (Ferrara, Italy). Patients were considered eligible if: on invasive mechanical ventilation;

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recovering from ARF; triggering the ventilator; and having Richmond Agitation Sedation Scale score between −1 and + 1. Patients were excluded if: contraindicated for esophageal catheter insertion; cardiac instability (heart rate > 120 beats/min, systolic blood pressure < 90 or > 160 mmHg and vasopressor infusion (i.e., dobutamine >5 μg/kg/min or noradrenaline >0.1 μg/kg/min)); neurological or neuromuscular pathology; elevated intracranial pressure; <18 years and pregnancy. This was a prospective single-center crossover study. The study was approved by the local ethics committee and informed consent obtained.

2.2. Clinical decision support system

An open-loop CDSS (Beacon Caresystem™, Mermaid Care A/S, Nørresundby, Denmark) was connected to the patient by pulse oximeter and respiratory tube including pneumotach measurement and side stream gas analysis. This allows measurement of oxygenation (SpO_2), RR, minute ventilation (VMIN), VT, fraction of end-tidal carbon dioxide ($FetCO_2$), fraction of end tidal oxygen ($FetO_2$), oxygen consumption (VO_2), carbon dioxide production (VCO_2) and respiratory exchange ratio (RER). The CDSS registers ventilator settings by serial communication with the ventilator. The CDSS was set to provide advice on FIO_2 and PS. For a more detailed description of the CDSS see the electronic supplementary material (ESM) and [7].

2.3. Procedure

The study was designed to investigate the CDSS response to systematic over and under support. Patients were studied semi-recumbent, and ventilated with a Servo i ventilator (Maquet Critical Care, Solna, Sweden) in PS mode. As support for respiratory muscles is a combination of levels of PS and PEEP, patients were randomized to receive over support (150% baseline) and under support (50% baseline), either with changes in PS or PEEP, with baseline settings those of the attending physician. Patients were randomized to receive over or under support first, with baseline ventilation for 15 min between phases (Fig. 1). Randomization was performed using closed envelopes.

CDSS advice was followed from baseline, and from over and under support. Advice was followed for maximum 1 h or five pieces of advice per phase, with a maximum duration of 6 h. Advice was followed if considered safe by the clinician, with unsafe advice documented.

2.4. Data collection and analysis

Patient characteristics (age, height, weight, sex, reasons for admission and intubation, morbidity, heart rate, MAP, adjunctive therapies, comorbidities, outcome and length of stay) were registered on inclusion. The CDSS registered advice, changes in settings and resulting changes in SpO_2, $FetCO_2$, RR and VT. Predicted body weight (PBW) and VT per PBW (VT/PBW) were calculated as previously [8]. VMIN and rapid shallow breathing index (RR/VT) were calculated from VT and RR. Each measurement represented a 2-min average.

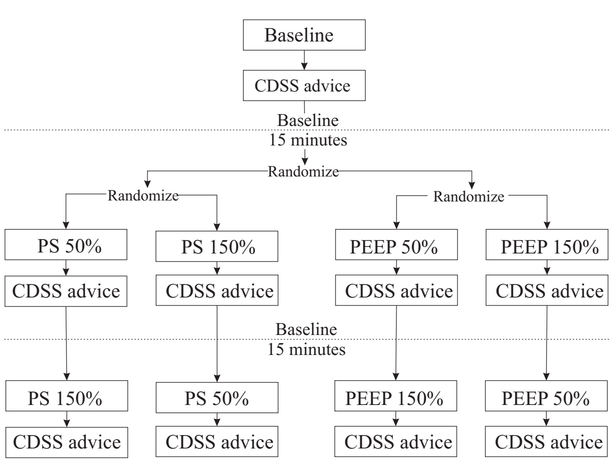

Fig. 1. Protocol flowchart.

Esophageal pressure (Pes) was measured using a standard air-filled balloon catheter (Microtek, Zutphen, The Netherlands). Proper positioning was verified by end expiratory occlusion (Baydur test) [9]. Airflow (V′) was measured with a heated pneumotachograph (3700, 0–160 l/min, Hans Rudolf, Kansas City, Mo., USA) placed between y-piece and endotracheal tube connected to a differential pressure transducer (DP55 ± 3.5 cmH_2O Raytech Instruments, B.C., Canada). Airway pressure (Paw) was measured through a side port on the pneumotachograph using a differential pressure transducer (DP55 ± 100 cmH_2O Raytech); and esophageal pressure (Pes) was measured by direct connection of a similar transducer to the catheter. Transpulmonary pressure (PL) was obtained by subtracting Pes from Paw.

VT, inspiratory time (Ti), RR, and the "duty cycle" (Ti/Ttot) were calculated offline as averages from flow traces. PL was used to calculate dynamic lung elastance ($E_{L,dyn}$) and pulmonary resistance ($R_{L,dyn}$) according to the Neergaard-Wirtz elastic subtraction technique [10].

The values for Pes at zero flow were assumed to be the beginning and end of inspiration. The theoretical value for chest wall compliance, i.e. 4% of the predicted value of the vital capacity per cmH_2O, was used, assuming no abnormal chest wall compliance [11]. Dynamic intrinsic PEEP ($PEEPi_{,dyn}$) was computed as the negative deflection in Pes from the onset of inspiratory effort to the point of zero flow during spontaneous inspiratory activity. The onset of inspiratory effort was determined as the beginning of the esophageal pressure decay at the end of expiration. The pressure time product (PTP) of the inspiration was calculated as the area subtended by Pes and the chest-wall static recoil pressure time, taking into account $PEEPi_{,dyn}$ [12].

Maximum inspiratory pressure (MIP) was obtained from the negative deflection in Paw during a maneuver of maximum inspiratory efforts against occluded airways for 20 s [20]. The Tension Time index of the inspiratory muscle (TTies) was calculated as described previously, i.e. $TTies = \frac{mean\ Pes}{MIP} * \frac{Ti}{Ttot}$ [13].

The waveforms of Paw, Pes and V′ were recorded continuously (Dyrec System, Raytech Instruments, B.C., Canada) at 100 Hz for offline data analysis. Paw, Pes and V′ were calculated as averages of 20 breaths immediately prior to ventilator change and 5–10 min after change. A customized version of software was used to analyse esophageal signals (ICU Lab software; Kleistek Engineering; Bari, Italy).

2.5. Statistical analysis

Statistical analysis was performed with SPSS (SPSS Statistics 22.0, IBM). Normality was tested using the Shapiro Wilk test. Descriptive statistics are reported as mean ± SD for normally distributed data and as median [interquartile range] for non-normally distributed data.

Values of ventilator settings and physiological variables were compared at baseline, over and under support, and before and after CDSS advice using either two-way repeated measures ANOVA for normally distributed measurements; or two way repeated measures non-parametric Friedman analysis. For variables with significance on ANOVA or Friedman analysis, post-hoc analysis was performed for differences between baseline values and over and under support; and differences due to CDSS advice from baseline, over and under support. Post-hoc comparisons were performed using paired *t*-test for normally distributed variables, or Wilcoxon, both with Bonferroni correction.

To investigate whether low values of PS advised by the CDSS were consistent with subsequent rapid extubation, a post-hoc analysis was performed comparing the subsequent clinical management of patients where advice following under-support resulted in low PS levels (PS ≤ 4 cmH_2O), or otherwise (PS > 4 cmH_2O).

Aliverti et al. [14] have previously shown that a pressure support change of 50%, from 10 to 15 cmH_2O, resulted in change in diaphragm muscle pressure of 1 cmH_2O. Assuming similar changes, a two-tailed, paired sample *t*-test with α-level of 0.05 showed that 19 patients were required in each arm to achieve statistical power of 0.9. Power analysis was performed with G*Power version 3.1.7 [15]. The study was terminated early, with data from the PS arm illustrating sufficient statistical power with 15 patients. Data from the PEEP arm illustrated very little effect in 8 patients, such that full inclusion would likely not result in clinical or statistical significance. For both arms care was taken to reduce the number patient numbers to a minimum to limit the need for potentially stressful reductions in settings.

3. Results

3.1. Patients

Patients' demographics data and clinical diagnosis are reported in Table 1

Table 1
Clinical characteristics of the patients and study start measurements.

Measured variable	Value
Total Number of patients	23
Age, yrs	72 [65–77]
Weight, kg	79 ± 15
BMI, kg m^{-2}	27.3 ± 5.0
Male, n (%)	18 (78)
Smoking history, n (%)	
Actual smoker	6 (26)
Former smoker	5 (22)
Comorbidities, n (%)	
COPD	7 (30)
Chronic kidney disease	4 (17)
Hypertension	16 (70)
Ischemic heart disease	8 (35)
Arrhythmia	4 (17)
Chronic heart failure	8 (35)
Peripheral vascular disease	6 (26)
Diabetes mellitus	5 (22)
Neurological disease	6 (26)
Chronic liver disease	4 (17)
Cancer	5 (22)
ICU admission reasons, n (%)	
Pneumonia	6 (26)
Septic shock	5 (22)
Peritonitis	4 (17)
Post-operative respiratory failure	3 (13)
Coma	3 (13)
Cardiac arrest	1 (4)
Hemorrhagic shock	1 (4)
SOFA score at ICU admission	7 [4–10]
SOFA score at study inclusion	7 [6–9]
SAPS II score at ICU admission	42 ± 12
PS level at ICU admission, cmH_2O	8.5 ± 2.7
PEEP at ICU admission, cmH_2O	7.7 ± 2.5
FiO_2 at ICU admission, %	51 ± 12
LIS score at ICU admission	2.5 ± 0.7
PF ratio at ICU admission	175 [123–275]
PF ratio study inclusion	210 [121–275]
Length of MV until inclusion, days	3 [2–7]
Length of MV after inclusion, days	6 [3−11]
Reintubation rate after study, n (%)	1 (6)
Total length of MV, days	10 [7–15]
ICU length of stay, days	12 [9–20]
ICU mortality, n (%)	4 (17)
Hospital length of stay, days	29 [21–45]
Hospital mortality, n (%)	7 (30)
Tracheostomy, n (%)	4 (17)

BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; SOFA = sequential organ failure assessment; SAPS = Simplified Acute Physiology Score; PS = pressure support; PEEP = positive end-expiratory pressure; FiO_2 = fraction of inspired oxygen; LIS = lung injury score; PF = arterial oxygen partial pressure to fraction of inspired oxygen ratio; MV = mechanical ventilation.

3.2. PS changes

Table 2 illustrates the effects of over and under support with PS, and the results of CDSS advice. Fig. 2 illustrates individual patient values of TTies, VT and RR/VT ratio. All advice was considered safe and applied.

3.3. Physiological response to PS changes

Over support (150% baseline) resulted in a tendency to decrease PTP (median 149 to 97 (cmH_2O s)/min), decrease TTies (mean 0.090 to 0.049), and a tendency to increase VT (8.6 to 10.1 ml/kg). No significant changes were seen in metabolic measurements, SpO_2 or $FetCO_2$. Under support (50% baseline), resulted in an tendency to increase PTP (median 149 to 195 (cmH_2O s)/min), and an increase in TTies (mean 0.090 to 0.120). No significant changes were seen in VT or RR, with a small but significant increase in $FetCO_2$. No significant changes were seen in metabolic measurements or SpO_2. Neither over or under support significantly modified $PEEPi_{,dyn}$.

3.4. Physiological response to CDSS advice in PS arm

CDSS advice from baseline resulted in significant reduction in PS (median 8 to 6 cm H_2O), with PS reduced below 8 cm H_2O in 5 of 15 patients. This resulted in small but insignificant increases in PTP and TTies, and no significant changes in VT, RR, $FetCO_2$ or metabolic measurements. Advice resulted in significant reduction in FIO_2 from a median of 50 to 36%, leading to significant reduction in SpO_2 from 98 to 96%.

CDSS advice from over support resulted in significant reduction in PS from a median of 12 to 6 cmH_2O, with PS reduced below 8 cm H_2O in 8 of 15 patients. This decrease resulted in significant increases in PTP (median 97 to 151 (cm H_2O s)/min) and TTies (mean 0.049 to 0.076), with a tendency to increase these to the levels following advice from baseline. Advice showed a tendency to reduce VT from median 10.1 to 8.9 ml/kg PBW a value not significantly different to that following advice from baseline. No significant differences were seen in RR, $FetCO_2$ or metabolic measurements. Advice resulted in a significant reduction in FIO_2 from median 50 to 38%, with a tendency to reduce SpO_2 from 97 to 95.8%.

CDSS advice from under support resulted in no significant changes in PTP or TTies, with these values not significantly different to values following advice from baseline, however with an increase in PS and reduction in TTies for a single patient with TTies above 0.20 following under support (Fig. 2). No significant differences were seen in VT, RR, $FetCO_2$ or metabolic measurements, either following advice or in comparison to the results of advice at baseline. Advice resulted in a significant reduction in FIO_2 from median 50 to 34%, leading to a significant reduction in SpO_2 from 98 to 95.9%. CDSS advice did not significantly modify $PEEPi_{,dyn}$ from baseline over or under support. In 9 patients (23%), PS levels following advice from under support were low (PS ≤ 4 cmH_2O), with these patients being extubated significantly faster following conclusion of this study (Table 3).

3.5. PEEP changes

Table 4 illustrates baseline levels and the effects of over and under support with PEEP, and the results of CDSS advice. All advice was considered safe, and applied.

Neither over (PEEP 150% Baseline) or under support (PEEP 50% Baseline), resulted in significant changes in variables describing respiratory muscle function, ventilation or respiratory gases. CDSS advice resulted in small non-significant reductions in PS from baseline, over and under support, with reduction greatest for over support. The small reduction in PS did not result in any significant changes in respiratory muscle function, ventilation or respiratory gases. Baseline FIO_2 values were about 40% and CDSS advice resulted in no significant change in either FIO_2 or SpO_2.

Table 2
Values of ventilator settings and physiological variables, at baseline, over and under support with PS, and before and after CDSS advice.

Measured variable	Baseline	Over support	Under support
Ventilator settings			
PS level, cmH_2O	8.0 [6–10]	12.0 [9–15]	4.0 [3–5]
PS level advice, cmH_2O	6.0 [3−10]	6.0 [6–12] (p = .035) #	4.0 [3–7] (p = .275) §
p-value*	p = .04	p = .005	p = .75
Breathing pattern			
VT, ml/kg PBW	8.6 ± 3.0	10.1 ± 2.9 (p = .08) #	8.6 ± 3.0 (p = 1.0) §
VT advice, ml/kg PBW	8.4 ± 2.8	8.9 ± 2.4 (p = 1.0) #	8.7 ± 3.0 (p = 1.0) §
p-value*	p = 1.0	p = .08	p = 1.0
RR, bpm	18.0 ± 6.4	14.7 ± 5.0 (p = .168) #	18.2 ± 7.6 (p = 1.0) §
RR advice, bpm	17.8 ± 6.6	15.7 ± 4.4 (p = .94) #	18.0 ± 7.5 (p = 1.0) §
p-value*	p = 1.0	p = .95	p = 1.0
RR/VT, bpm/L	29 [24–54]	23 [16–35] (p = .014) #	28 [17–62] (p = 1.0) §
RR/VT advice, bpm/L	29 [23–54]	30 [21–35] (p = 1.0) #	29 [17–55] (p = 1.0) §
	p = 1.0	p = .21	p = 1.0
TI, sec	1.1 ± 0.2	1.4 ± 0.5 (p = .18) #	1.1 ± 0.3 (p = 1.0) §
TI advice, sec	1.1 ± 0.2	1.3 ± 0.3(p = .35) #	1.1 ± 0.3 (p = 1.0) §
p-value*	p = 1.0	p = 1.0	p = 1.0
Ti/Ttot, %	31 ± 7	31 ± 8	30 ± 6
Ti/Ttot advice, %	31 ± 7	31 ± 6	30 ± 6
Respiratory mechanics			
$PEEP_{i,dyn}$, cmH_2O	1.3 [0.5–1.6]	1.1 [0.5–1.3]	1.6 [0.7–2.1]
$PEEPi_{,dyn}$ advice, cmH_2O	1.6 [0.5–2.2]	1.1 [0.7–1.3]	1.5 [0.6–1.5]
$R_{L,dyn}$, $cmH_2O/L/s$	17.5 ± 5.0	17.3 ± 3.1 (p = 1.0) #	15.1 ± 3.7 (p = .175) §
$R_{L,dyn}$ advice, $cmH_2O/L/s$	15.9 ± 5.5	15.4 ± 4.1 (p = 1.0) #	15.4 ± 4.0 (p = 1.0) §
p-value*	p = .014	p = .28	p = 1.0
$E_{L,dyn}$ cmH_2O/L	17.8 ± 8.9	15.8 ± 8.6 (p = .042) #	17.6 ± 10.7 (p = 1.0) §
$E_{L,dyn}$ advice, cmH_2O/L	18.5 ± 8.7	16.9 ± 8.5(p = .37) #	17.1 ± 9.0 (p = .28)
p-value*	p = 1.0	p = .53	p = 1.0
Esophageal pressure measurements			
TTies	0.090 ± 0.028	0.049 ± 0.030 (p < .01) #	0.120 ± 0.044 (p = .007)§
TTies advice	0.103 ± 0.041	0.076 ± 0.038 (p = .08) #	0.113 ± 0.038 (p = .609) §
p-value*	p = .616	p < .01	p = 1.0
PTP_{min}, (cmH_2O*s)/min	149 [108–204]	97 [26–125] (p = .07) #	195 [163–228] (p = .063) §
PTP_{min} advice, (cmH_2O*s)/min	187 [114–221]	151 [73–166](p = .056) #	187 [168–228](p = 1.0) §
p-value*	p = .33	p = .021	p = 1.0
Respiratory gas			
$FetCO_2$, %	5.10 ± 0.86	5.07 ± 0.79 (p = 1.0) #	5.24 ± 0.97 (p = .028)§
$FetCO_2$ advice, %	5.20 ± 0.91	5.19 ± 0.93 (p = 1.0) #	5.23 ± 0.92 (p = 1.0)§
p-value*	p = .175	p = .53	p = 1.0
Metabolism			
VO_2, L/min	0.23 [0.21–0.26]	0.22[0.19–0.27](p = .53)#	0.22 [0.19–0.25](p = 1.0)§
VO_2 advice, L/min	0.22 [0.19–0.25]	0.20 [0.16–0.24](p = .189)#	0.22 [0.19–0.25](p = 1.0)§
p-value*	p = .581	p = .252	p = 1.0
VCO_2, L/min	0.19 [0.17–0.20]	0.17 [0.15–0.21]	0.18 [0.15–0.20]
VCO_2 advice, L/min	0.19 [0.15–0.22]	0.17 [0.14–0.19]	0.18 [0.15–0.20]
RER	0.80 ± 0.06	0.81 ± 0.08	0.80 ± 0.08
RER advice	0.82 ± 0.08	0.85 ± 0.09	0.80 ± 0.11
Oxygenation			
FIO_2, %	50 [45–60]	50 [45–60]	50 [45–60]
FIO_2 advice, %	36 [35–51]	38 [35–45] (p = 1.0) #	34 [30–42] (p = .7) §
p-value*	p = .005	p = .005	p = .005
SpO_2, %	98.0 [95.5–99]	97.0 [94.8–99.0] (p = 1.0)#	98.0 [96.1–99.2] (p = 1.0)§
SpO_2 advice, %	96.0 [94.2–96.8]	95.8 [93.0–97.4] (p = 1.0)#	95.9 [94.3–97.1] (p = 1.0)§
p-value*	p = .021	p = .077	p = .014

PS, pressure support; VT, tidal volume; RR, respiratory rate; Ti, inspiratory time; Ttot, total respiratory time; $PEEP_{i,dyn}$, dynamic intrinsic positive end expiratory pressure; $R_{L,dyn}$, dynamic resistance of the lung; $E_{L,dyn}$, dynamic elastance of the lung; TTies, tension-time index of the respiratory muscles; PTP_{min}, pressure time product per minute. $FetCO_2$, end tidal CO_2 fraction; VO_2, oxygen consumption; VCO_2, carbon dioxide production; RER, respiratory exchange ratio; FIO_2, inspired O_2 fraction; SpO_2, peripheral capillary oxygen saturation. Normally distributed variables are expressed as mean ± standard deviation, non-normal ones as median [interquartile range].

* Comparison between study protocol steps and CDSS final advice (unpaired Student's*t*-tests or Mann– Whitney *U* test). Values only given where ANOVA or Friedman analysis significant.

\# Comparison between baseline and over support.

§ Comparison between baseline and under support (unpaired Student's *t*-tests or Mann– Whitney U test; P < .05).

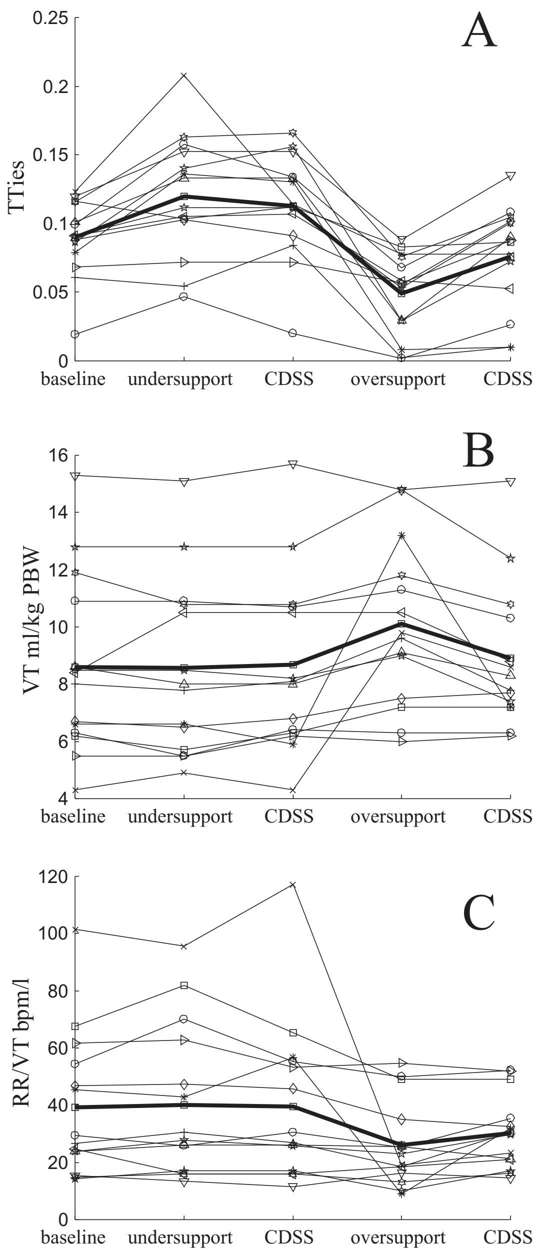

Fig. 2. A) Tension time index (TTies) of the respiratory muscles, B) tidal volume (VT), and C) respiratory rate/tidal volume ratio (RR/VT), at baseline PS, following under support with PS, following CDSS advice subsequent to under support, following over support with PS, and following CDSS advice subsequent to over support. Thin lines - individual patients, bold lines – mean.

Table 3
Clincal characteristics in patients with low PS level (≤4 cm H_2O) or otherwise, following advice from under support.

	PS undersupport >4 ($n = 6$)	PS undersupport ≤4 ($n = 9$)	p-Value
SAPS II at ICU admission	48 [41–60]	40 [34–49]	0.145
SOFA score at study inclusion	8 [7–9]	5 [5–10]	0.224
PF ratio study inclusion	138 [114–190]	260 [153–295]	0.066
Length of MV, days	15 [12–29]	8 [5–11]	0.008
Length of MV after inclusion, days	13 [6–14]	3 [2–7]	0.012
ICU length of stay, days	21 [15–31]	10 [8–12]	0.026
Hospital length of stay, days	53 [32−122]	23 [14–45]	0.026

4. Discussion

This study shows that the advice of an open-loop CDSS reduced the negative effects of over and under support by modifying PS, and significantly reducing FIO_2 while maintaining clinically acceptable SpO_2.

Physiological changes to over and under support were most pronounced in PS over support, where all measurements of respiratory muscle function were reduced. In particular, TTies was reduced from median 0.090 to 0.049. Over support resulted in a tendency to increase VT from median 8.6 to 10.1 ml/kg PBW, values that may increase the risk of lung damage [8] due to passive lung inflation [2,16]. Under support resulted in significant increase in TTies. However, the lack of a dramatic increase in TTies is consistent with no significant changes in VO_2, VCO_2 or RR/VT following under support.

Adjusting ventilator settings according to CDSS advice reduced PS significantly from baseline and over support. In 5 of 15 patients (33%) from baseline, and 8 of 15 patients (53%) from over support, PS was reduced to a value below 8 cm H_2O. As suggested previously [6], these results may indicate that the CDSS successfully reduced PS levels to those where extubation is not prohibited. These reductions from over support increased esophageal measurements of breathing effort with TTies increasing from 0.049 to 0.076, and showed a tendency to reduce passive lung inflation with VT reducing from 10.1 to 8.9 ml/kg PBW, a value not significantly different from baseline. Both indicate reduced likelihood of respiratory muscle atrophy.

CDSS advice did not increase median PS following under support, although there was an increase in the upper end of the inter-quartile range. When interpreting the values of TTies on under support, and following subsequent CDSS advice, it is important to note that in the present study we evaluated tension time index calculated from the esophageal pressure swings, and as such included in our evaluation the breathing effort of all contributing respiratory muscles including the diaphragm and rib cage muscles. The tension-time index fatigue threshold for the diaphragm (TTidi) can be calculated from transdiaphragmatic pressure, and has previously been defined as 0.15–0.18 in healthy subjects during loaded breathing [16]. The tension time index threshold of healthy subjects trained to breath only with rib cage muscles illustrated a fatigue threshold for these muscles of 0.30 [17]. It is not possible from our measurements to differentiate between diaphragm and rib cage muscle activity, however, as previously demonstrated by Parthasarathy et al. in patients undergoing weaning from mechanical ventilation, patients predominantly recruit both the diaphragm and accessory respiratory muscles, with accessory muscle contribution being greater during weaning failure compared to success [18]. Recently, Walterspacher et al. reported electrical muscle activity of both diaphragm and rib cage muscles in weaning failure patients, and found that the diaphragm respiratory drive depended on body posture, with diaphragm activity reducing as patients moved from supine to semi-recumbent to sitting [19]. The patients studied in the present study were all in the supine or semi-recumbent position and tolerated the pressure support reductions well. As such, they were likely breathing using both diaphragm and rib cage muscles, with an expected fatigue threshold reflecting both these muscle groups, that is between 0.18 and 0.30. The mean values of TTies $= 0.113 \pm 0.038$ and 0.076 ± 0.038 seen in this study following under and over support respectively, are therefore below the limit considered to avoid respiratory muscle fatigue. The lack of substantial advice to increase PS following under support is consistent with this TTies threshold and the patients' physiological and clinical state. Indeed, only one patient had a value of TTies suggesting elevated risk of fatigue following under support (TTies $= 0.21$). In this patient, CDSS advice increased PS and reduced TTies to 0.12, but without reducing RR/VT ratio, which cannot be considered a specific marker of fatigue [20]. From a clinical perspective, patients with low values of PS following advice were extubated more quickly, and had significantly fewer days on mechanical ventilation. Neither under support or advice from under support resulted in significant changes in VT, RR or RR/VT, apart from the patient with

Table 4
Values of ventilator settings and physiological variables, at baseline, over and under support with PEEP, and before and after CDSS advice.

Measured variable	Baseline	Over PEEP support	Under PEEP support
Ventilatory settings			
PS level, cmH_2O	8.5 ± 3.5	8.5 ± 3.5	8.5 ± 3.5
PS level advice, cmH_2O	7.5 ± 3.7	7.1 ± 3.4 (*p* = *1.0*)#	7.8 ± 4.1 (*p* = *1.0*) §
p-value*	*p* = *.350*	*p* = *.315*	*p* = *.777*
PEEP, cmH_2O	7.9 ± 2.2	12.1 ± 3.1	4.0 ± 1.1
PEEP - PS advice, cmH_2O	7.9 ± 2.2	12.1 ± 3.1	4.0 ± 1.1
Breathing patterns			
VT, ml/kg PBW	8.3 ± 3.3	8.5 ± 3.3	7.7 ± 2.9
VT advice, ml/kg PBW	7.9 ± 2.4	7.7 ± 2.8	7.5 ± 2.7
p-value*			
RR, bpm	17.1 ± 3.6	16.1 ± 3.4 (*p* = *.952*)#	18.7 ± 3.6 (*p* = *1.0*) §
RR advice, bpm	16.6 ± 3.5	17.0 ± 3.9 (*p* = *1.0*)#	19.2 ± 3.1 (*p* = *.371*) §
p-value*	*p* = *1.0*	*p* = *1.0*	*p* = *1.0*
RR/VT, bpm/L	36 ± 21	38 ± 19	30 ± 15
RR/VT advice, bpm/L	34 ± 16	33 ± 18	27 ± 12
Ti, sec	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.2
Ti advice, *sec*	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.2
Ti/Ttot, %	32 ± 6	32 ± 7	34 ± 7
Ti/Ttot advice, %	32 ± 7	32 ± 8	35 ± 6
Respiratory mechanics			
PEEPi, cmH_2O	0.6 [0.2–1.3]	0.6 [0.3–1.3]	0.8 [0.3–1.5]
PEEPi,advice, cmH_2O	0.4 [0.2–0.9]	0.6 [0.3–1.1]	0.8 [0.2–2.5]
$R_{L,dyn}$, $cmH_2O/L/s$	18.2 ± 9.4	17.6 ± 8.2	19.3 ± 10.4
$R_{L,dyn}$ advice, $cmH_2O/L/s$	17.2 ± 9.4	17.6 ± 8.2	18.9 ± 10.6
$E_{L,dyn}$, cmH_2O/L	19 [11–27]	20 [11–25]	22 [9–45]
$E_{L,dyn}$ advice, cmH_2O/L	20 [11–27]	18 [11–24]	22 [9–45]
Esophageal pressure measurements			
TTies	0.067 ± 0.035	0.062 ± 0.044	0.077 ± 0.033
TTies advice	0.070 ± 0.034	0.066 ± 0.043	0.083 ± 0.040
PTP_{min}, (cmH_2O*s)/min	142 ± 99	139 ± 125	153 ± 83
PTP_{min} advice, (cmH_2O*s)/min	143 ± 90	141 ± 115	164 ± 87
Respiratory gas			
$FetCO_2$, %	0.057 ± 0.011	0.058 ± 0.012	0.057 ± 0.004
$FetCO_2$ advice, %	0.057 ± 0.011	0.058 ± 0.011	0.058 ± 0.011
Metabolism			
VO_2, L/min	0.25 ± 0.07	0.25 ± 0.08	0.26 ± 0.08
VO_2 advice, L/min	0.23 ± 0.07	0.24 ± 0.07	0.25 ± 0.09
VCO_2, L/min	0.20 ± 0.05	0.20 ± 0.06	0.21 ± 0.08
VCO_2 advice, L/min	0.20 ± 0.04	0.20 ± 0.06	0.21 ± 0.08
RER	0.84 ± 0.05	0.82 ± 0.04	0.78 ± 0.07
RER advice	0.87 ± 0.09	0.85 ± 0.06	0.83 ± 0.10
Oxygenation			
FIO_2, %	40 [40–55]	40 [40–55]	40 [40–55]
FIO_2 advice, %	40 [31–58]	40 [35–48]	40 [35–55]
SpO_2, %	95.9 ± 2.4	95.6 ± 2.9	95.6 ± 3.0.2
SpO_2 advice, %	95.6 ± 2.3	95.0 ± 1.8	95.0 ± 1.4

PS, pressure support; VT, tidal volume; RR, respiratory rate; Ti, inspiratory time; Ttot, total respiratory time; $PEEP_{i,dyn}$, dynamic intrinsic positive end expiratory pressure; $R_{L,dyn}$, dynamic resistance of the lung; $E_{L,dyn}$, dynamic elastance of the lung; TTies, tension-time index of the respiratory muscles; PTP_{min}, pressure time product per minute. $FetCO_2$, end tidal CO_2 fraction; VO_2, oxygen consumption; VCO_2, carbon dioxide production; RER, respiratory exchange ratio; FIO_2, inspired O_2 fraction; SpO_2, peripheral capillary oxygen saturation. Normally distributed variables are expressed as mean ± standard deviation, non-normal ones as median [interquartile range].

* Comparison between study protocol steps and CDSS final advice (unpaired Student's *t*-tests or Mann– Whitney *U* test). Values only given where ANOVA or Friedman analysis significant.

\# Comparison between baseline and over support.

§ Comparison between baseline and under support (unpaired Student's *t*-tests or Mann– Whitney *U* test; $P < .05$).

elevated TTies. In particular, values of VO_2 and VCO_2 were not significantly increased on under support or following advice. Brochard et al. have showed that both VO_2 and patient's work of breathing are increased 20 min after reducing PS in difficult to wean patients [2]. It seems likely then that the lack of increase in VO_2 seen in these patients on reducing PS for a similar period reflects a minimal increase in work of breathing in these patients.

In patients studied with over and under support of PS, CDSS advice reduced FIO_2 resulting in lower but safe SpO_2 (from median 98 to 96%). This advice can be seen as beneficial, with a recent study showing that median changes in FIO_2 from 39% to 36% to ensure SpO_2 from 94% to 98%, reduced ICU mortality from 20.2 to 11.6% [1]. In patients studied in the PEEP group, baseline FIO_2 levels were lower, explaining why CDSS FIO_2 advice did not differ from clinical practice.

The lack of effect of changing PEEP levels is consistent with the relatively low levels of $PEEPi_{,dyn}$ measured, where all but one patient had $PEEPi_{,dyn} < 3$ cmH_2O, and little effect of PEEP on either $R_{L,dyn}$ or $E_{L,dyn}$. The lack of substantial $PEEPi_{,dyn}$ in both groups would suggest little inspiratory threshold load on the respiratory muscles, and as such little response to PEEP changes.

A presentation of the physiological models included in the CDSS, including their structure, function and evaluation has been summarised recently [7], see ESM. Simulations performed using the models allow the user to review the potential response of the patient to ventilator changes before applying advice. Doing this as an "open-loop" system may promote understanding of the primary compromise when setting PS, this being to reduce PS to prevent VILI and respiratory muscle atrophy, while increasing PS to prevent patient respiratory muscle stress and fatigue.

Other systems are available for providing advice on ventilator settings in either an "open loop" fashion [21], or as "closed loop" systems directly controlling ventilator levels [22,23]. The advice of VentAssist (NM3 Monitor, Philips Healthcare, Eindhoven, The Netherlands) on PS has been shown to be similar to the decisions of attending physicians [21,24]). SmartCare (Dräger, Lübeck, Germany) [22] and ASV/IntelliVent-ASV (Hamilton Medical, Bonaduz, Switzerland) [23] regulate PS levels, and have been evaluated in randomized control trials (Smart Care [25-28], ASV [29,30]), with some of these studies illustrating that these systems can promote faster weaning from mechanical ventilation [26,30].

The major limitation of this study relates to the patients included, these probably being quite close to recovering from ARF and therefore different to those studied previously [31-33]. In this study patients had average SAPSII score of 42, similar to the average of 36.3 in general medical ICU's in Northern Italy [34]. The lack of dramatic response to under support with PS, or to changes in PEEP, is therefore interesting, suggesting that low levels of PS and PEEP could be tolerated. Indeed, it may be the case that many of these patients could have been considered for extubation, as indicated by reduction in PS below 8 cmH_2O following CDSS advice, and by rapid extubation in those where advice resulted in the lowest PS levels.

This study has shown that the advice of an open-loop physiological model based CDSS resulted in appropriate response to changes in PS, providing advice which resulted in low values of PS, often where extubation was not prohibited, while acting to preserve respiratory muscle function and to prevent passive lung inflation. The CDSS was able to minimize FIO_2 while maintaining SpO_2 at values that can be considered safe and beneficial.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.10.003.

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