Amsterdam University of Applied Sciences

A closed-loop ventilation mode that targets the lowest work and force of breathing reduces the transpulmonary driving pressure in patients with moderate-to-severe ARDS

Author(s)
Buiteman-Kruizinga, Laura A.; van Meenen, David M. P.; Bos, Lieuwe D. J.; van der Heiden, Pim L. J.; Paulus, Frederique; Schultz, Marcus J.

Creating Tomorrow

A closed-loop ventilation mode that targets the lowest work and force of breathing reduces the transpulmonary driving pressure in patients with moderate-to-severe ARDS

Laura A. Buiteman-Kruizinga[1,2]* , David M. P. van Meenen[2,3], Lieuwe D. J. Bos[2,4], Pim L. J. van der Heiden[1], Frederique Paulus[2,5] and Marcus J. Schultz[2,6,7]

*Correspondence:
l.kruizinga@rdgg.nl

[1] Department of Intensive Care, Reinier de Graaf Hospital, Delft, The Netherlands
[2] Department of Intensive Care, Amsterdam University Medical Centers, Location 'AMC', Amsterdam, The Netherlands
[3] Department of Anesthesia, Amsterdam University Medical Centers, Location 'AMC', Amsterdam, The Netherlands
[4] Department of Respiratory Medicine, Amsterdam University Medical Centers, Location 'AMC', Amsterdam, The Netherlands
[5] ACHIEVE, Centre of Applied Research, Faculty of Health, Amsterdam University of Applied Sciences, Amsterdam, The Netherlands
[6] Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand
[7] Nuffield Department of Medicine, University of Oxford, Oxford, UK

Abstract

Introduction: The driving pressure (ΔP) has an independent association with outcome in patients with acute respiratory distress syndrome (ARDS). INTELLiVENT-Adaptive Support Ventilation (ASV) is a closed-loop mode of ventilation that targets the lowest work and force of breathing.

Aim: To compare transpulmonary and respiratory system ΔP between closed-loop ventilation and conventional pressure controlled ventilation in patients with moderate-to-severe ARDS.

Methods: Single-center randomized cross-over clinical trial in patients in the early phase of ARDS. Patients were randomly assigned to start with a 4-h period of closed-loop ventilation or conventional ventilation, after which the alternate ventilation mode was selected. The primary outcome was the transpulmonary ΔP; secondary outcomes included respiratory system ΔP, and other key parameters of ventilation.

Results: Thirteen patients were included, and all had fully analyzable data sets. Compared to conventional ventilation, with closed-loop ventilation the median transpulmonary ΔP with was lower (7.0 [5.0–10.0] vs. 10.0 [8.0–11.0] cmH$_2$O, mean difference -2.5 [95% CI -2.6 to -2.1] cmH$_2$O; $P = 0.0001$). Inspiratory transpulmonary pressure and the respiratory rate were also lower. Tidal volume, however, was higher with closed-loop ventilation, but stayed below generally accepted safety cutoffs in the majority of patients.

Conclusions: In this small physiological study, when compared to conventional pressure controlled ventilation INTELLiVENT-ASV reduced the transpulmonary ΔP in patients in the early phase of moderate-to-severe ARDS. This closed-loop ventilation mode also led to a lower inspiratory transpulmonary pressure and a lower respiratory rate, thereby reducing the intensity of ventilation.

Trial registration Clinicaltrials.gov, NCT03211494, July 7, 2017. https://clinicaltrials.gov/ct2/show/NCT03211494?term=airdrop&draw=2&rank=1.

Buiteman-Kruizinga *et al. Intensive Care Medicine Experimental*   (2023) 11:42

Page 2 of 13

Background

The driving pressure (ΔP), an easy to calculate ventilation parameter [1, 2], represents the strain applied to the lung with each breath during invasive ventilation [3]. The ΔP has an independent association with outcome in critically ill invasively ventilated patients, including in patients with acute respiratory distress syndrome (ARDS) [4–6]. It has been proposed to adjust ventilator settings so that the ΔP becomes or remains low in patients with ARDS, using 15 cmH$_2$O as a safe cutoff [1, 7].

Closed-loop ventilation modes are increasingly available for use in critically ill invasively ventilated patients [8]. INTELLiVENT-Adaptive Support Ventilation (ASV) is one sophisticated form of automated, or closed-loop ventilation, wherein tidal volume (V_T), respiratory rate (RR), positive end-expiratory pressure (PEEP) and the fraction of inspired oxygen (FiO$_2$) are automatically set and adjusted by a series of algorithms within the ventilator that target a lower work of breathing and a lower force of breathing [9, 10]. INTELLiVENT-ASV then acts within ranges for the end-tidal CO$_2$ and the SpO$_2$, and limits for maximum airway pressure and PEEP, set by the ICU nurse or doctor. Previous studies of this closed-loop ventilation mode have shown a reduction in ΔP with its use, but studies so far included mixed patient groups [11], or exclusively included patients with coronavirus disease 2019 (COVID-19) ARDS [12, 13]. Also, none of these studies used an esophagus balloon catheter for proper measurements of transpulmonary pressures. Indeed, all these studies reported the effect of closed-loop ventilation on the ΔP of the respiratory system and not its effects on the transpulmonary ΔP [14].

We aimed to determine the effects of INTELLiVENT-ASV on transpulmonary ΔP and other ventilation parameters in patients in the early phase of moderate-to-severe ARDS. For this, we designed and conducted a cross-over study, named 'Does Automated closed-loop ventilation Reduce the DRiving Pressure levels in patients with ARDS (AiRDRoP)'. We hypothesized that the closed-loop ventilation of interest would reduce the transpulmonary ΔP.

Methods

Study design

This was an investigator-initiated, single-center, randomized cross-over clinical trial conducted at the intensive care unit (ICU) of the Amsterdam University Medical Centers, 'location AMC', in Amsterdam, the Netherlands. The study protocol was approved by the local Institutional Review Board (April 13, 2017; 2016_349#B2017211). The study protocol was registered at clinicaltrials.gov (study identifier NCT03211494). Written informed consent was obtained from a legal representative of the patient before inclusion and randomization. A statistical analysis plan was written and finalized before cleaning and closing of the database.

This study was originally designed to have two phases, one randomized cross-over phase, followed by a randomized parallel phase. We prematurely stopped the study

because of a sharp increase in use of extracorporeal life support (ELS) in patients with ARDS as part of change in the standard of care at the study site. This meant that it was no longer guaranteed that patients would not receive ELS, i.e., in the second part of the study. Consequently, we stopped inclusions of patients, as use of ELS was an exclusion criterion for this study. We also noticed that in many patients the esophagus balloon catheter was removed after the cross-over phase, because patients became active and doctors saw no need in keeping it in place.

Patients

Patents were eligible for participation in AiRDRoP if: (1) aged > 18 years; (2) having moderate-to-severe ARDS, according to the current definition for ARDS [15]. Patients were excluded if they were after 24 h following the initial diagnosis of ARDS, and in case of a contraindication for placing an esophagus balloon catheter. We also excluded pregnant patients, terminally ill patients, patients with increased or uncontrollable intracranial pressure, patients receiving therapies that could influence ventilator settings and parameters, and patients previously included in this study.

Randomization and masking

Patients were randomly assigned in a 1:1 ratio to start with closed-loop ventilation or conventional ventilation for 4 h, after which each patient received ventilation using the alternative ventilation mode. A dedicated, password protected, web-based randomization system (SSL-encrypted website, Sealed Envelope™, London, United Kingdom) was used for non-stratified block randomization using block sizes of 4 patients. Doctors and nurses taking care of the patients could not be blinded because of the nature of the intervention. The investigators analyzing the data, however, remained blinded for the allocated ventilation mode at all times.

Study interventions

Patients were sedated and if necessary paralyzed according to the local guidelines for analgo-sedation. All patients were to be without spontaneous breathing activity. To guarantee this, an experienced researcher checked the ventilator waveforms and compared set RR with measured RR at each time point data were to be collected. Patients were hemodynamically stabilized before start of the study, meaning that they had received intravenous fluids and if necessary norepinephrine or dobutamine, according to the local protocol.

The same type of ventilator (Hamilton Medical AG, Bonaduz, Switzerland), was used for all patients. All doctors and nurses within the department were extensively trained in use and qualified and experienced with this ventilator, and also the two ventilation modes that were compared.

An esophageal balloon catheter (Cooper Surgical, Trumbull, CT) was inserted, and correct position was confirmed with an occlusion test, as previously described [16]. The catheter was used for collection of pressure data during the cross-over phase of the study, but these data were not disclosed to the bedside doctors or nurses. In other words, they could not be used to adjust ventilator settings.

At initiation of invasive ventilation, the attending doctor or nurse set the ventilator according to the local ventilation protocol that dictates the use of lung-protective ventilator settings with conventional pressure controlled ventilation. Herein, ventilation should use a low V_T of 6–8 mL/kg predicted body weight (PBW) with a maximum airway pressure limit of 30 cmH$_2$O, and PEEP according to the lower PEEP/FiO$_2$ table [17]. The lowest PEEP allowed was 5 cmH$_2$O. FiO$_2$ was adjusted to maintain the peripheral oxygen saturation (SpO$_2$) between 92 and 96%. The respiratory rate was adjusted to maintain end-tidal CO$_2$ (etCO$_2$) to have an arterial pH between 7.25 and 7.45.

At start of closed-loop ventilation, the attending doctor or nurse set the peripheral pulse oximetry (SpO$_2$) and end-tidal CO$_2$ (etCO$_2$) ranges using the same goals as with conventional ventilation. The closed-loop ventilation mode then automatically adjusted V_T, RR, PEEP and FiO$_2$ according to a series of software algorithms that continuously target a low work of breathing and a low force of breathing, as previously described [9, 10]. With closed-loop ventilation, the PEEP window was set at 5 to 15 cmH$_2$O with a maximum airway pressure limit of 30 cmH$_2$O. With start of conventional ventilation, the attending doctor or nurse set the ventilator as described at initiation of invasive ventilation.

Data collection

Ventilation parameters were collected at the bedside at 32 consecutive time points, 16 time points per each ventilation mode. Every 15 min, at all time points, inspiratory holds and expiratory holds were performed to measure the static ventilation pressures. We collected end-inspiratory airway pressure (Pplat, cmH$_2$O), end-inspiratory esophageal pressure (cmH$_2$O, inspiratory Pes), end-expiratory airway pressure (PEEP, cmH$_2$O), and end-expiratory esophageal pressure (cmH$_2$O, expiratory Pes). We also collected measured and set respiratory rate (RR, breaths per minute), tidal volume (V_T, mL), fraction of inspired oxygen (FiO$_2$), end-tidal carbon dioxide (etCO$_2$, kPa) and pulse oximetry (SpO$_2$, %). In addition, an arterial blood gas was performed 30 min before the end of the block, according to the study protocol.

Outcomes

The primary outcome was the transpulmonary ΔP (ΔP_{TP}). Secondary outcomes included V_T, respiratory system ΔP (ΔP_{RS}), respiratory system compliance (C_{RS}), inspiratory transpulmonary pressure (P_{TP}), PEEP, Pplat and RR.

Calculations

The following equations were used [1, 18–20]:

$$V_T\left(\text{mL/kg PBW}\right) = V_T/\text{PBW}; \tag{1}$$

$$C_{RS}(\text{mL/cmH}_2\text{O}) = V_T/(\text{Pplat}-\text{PEEP}); \tag{2}$$

$$\Delta P_{RS}(\text{cmH}_2\text{O}) = \text{Pplat}-\text{total PEEP}; \tag{3}$$

$$\Delta P_{ES}(cmH_2O) = \text{inspiratory Pes} - \text{expiratory Pes};\tag{4}$$

$$\Delta P_{TP}(cmH_2O) = \Delta P_{RS} - \Delta P_{ES};\ \text{and}\tag{5}$$

$$P_{TP}(cmH_2O) = \text{Pplat} - \Delta P_{ES}.\tag{6}$$

Sample size calculation

We based the power calculation for the randomized cross-over phase of the study on unpublished data from a published cohort of ARDS patients [21], and data from one presented scientific abstract [22]. The power calculation showed that 12 patients would be needed to have 80% statistical power to detect a difference in the ΔP_{TP}, assuming an effect size (*f*) of 0.25. This number was reached at the moment the study was primarily stopped.

Statistical analysis

Data are expressed in numbers and proportions for categorical variables and medians [with interquartile ranges] or means (with standard deviations) for continuous variables, where appropriate. Proportions are compared using Chi-squared test or Fisher exact as required by variable distribution; continuous variables are compared using paired *T*-test or Wilcoxon signed-rank where appropriate. Effects are presented with a 95% confidence interval (95% CI).

A repeated measure analysis of variance (ANOVA) was performed to evaluate the effect of ventilation mode over time, to account for the repeated measurements and the time exposure, on ΔP_{TP}, ΔP_{RS} and the other collected ventilation parameters. We performed pairwise comparisons to evaluate the effect of ventilation mode at the individual time points.

Cumulative distribution plots, boxplots, scatterplots and line plots were constructed to visualize ΔP_{TP}, ΔP_{RS} and other ventilation parameters with closed-loop ventilation versus conventional ventilation. In the cumulative distribution plots, vertical dotted lines represent the median of the corresponding value with conventional ventilation, and horizontal dotted lines show the respective proportion of patients reaching each cutoff. In addition, the relationship between ventilation parameters was visualized in plots using least squares method regression.

We performed two post hoc analyses, one wherein we compared respiratory system mechanical power (MP_{RS}) and transpulmonary MP (MP_{TP}) with closed-loop ventilation to conventional ventilation. We calculated MP_{RS} [23], MP_{TP} [24, 25] and lung elastance (E_L) [24] as follows:

$$MP_{RS}(J/min) = 0.098 * RR * V_T * \left(\text{Ppeak} - \tfrac{1}{2} * \Delta P\right);\tag{7}$$

$$MP_{TP}(J/min) = 0.098 * RR * \left(V_T^2 * \tfrac{1}{2} * E_L + V_E * PEEP\right);\tag{8}$$

$$E_L(cmH_2O/L) = \Delta P_{TP}/V_T.\tag{9}$$

In the second post hoc analysis, we used a generalized linear mixed model analysis to improve the inclusion of the effect of time on the ventilation parameters in the analysis, with ventilation mode and time as fixed effects, and patients as random effect.

For the pairwise comparisons, an adjusted *P* value was calculated using Bonferroni method, and a $P < 0.003$ was considered significant. A $P < 0.05$ was considered significant for the other analyses. Missing data were < 1% and imputed with multivariate imputation via chained equations (MICE) by means of predictive mean matching method [26].

All analyses were performed in R version 4.0.3 (R Foundation, Vienna, Austria).

Results

Patients

Between November 3, 2017 and March 1, 2019, 13 patients were included (Fig. 1). The majority of patients were male (62%), the main cause for ARDS was sepsis (Table 1). All patients completed the cross-over phases of the study and were ventilated and switched according to the randomization arm. There were no protocol violations, meaning that patients were ventilated according to randomization at all time points. 5 patients started with closed-loop ventilation, 8 patients started with conventional ventilation.

Transpulmonary driving pressure

Compared to conventional ventilation, with closed-loop ventilation the median ΔP_{TP} was lower (7.0 [5.0–10.0] versus 10.0 [8.0–11.0] cmH$_2$O (mean difference -2.5 [95% CI -2.6 to -2.1] cmH$_2$O; $F(1,11) = 33.204$; $P = 0.0001$) (Table 2, Figs. 2 and 3). The ventilation mode had a significant effect which did not change with time ($P = 0.15$) nor with the interaction of ventilation mode*time ($P = 0.78$).

Other ventilatory parameters

Compared to conventional ventilation, with closed-loop ventilation the median ΔP_{RS} was not different (Table 2, Figs. 2 and 3). With the closed-loop mode, median ΔP_{RS}
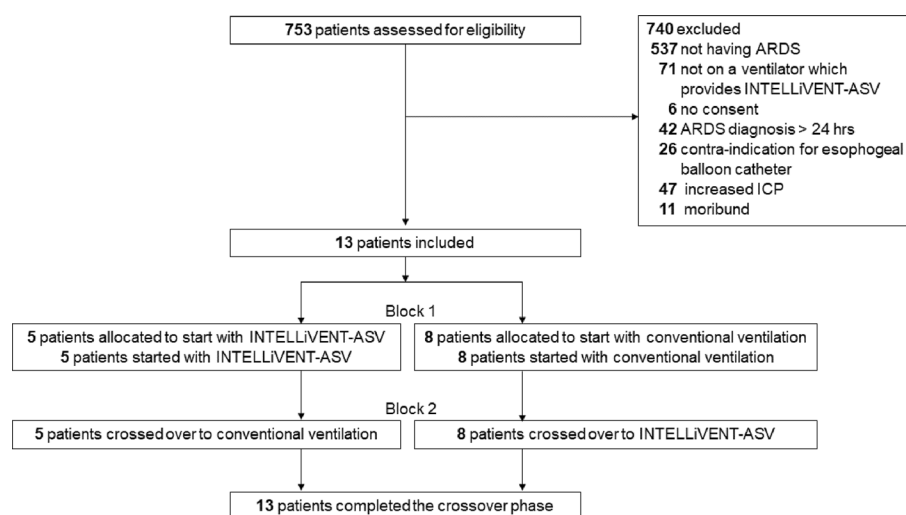
Fig. 1 Flow of patients in the study

Table 1 Baseline characteristics

	$N=13$
Gender, male	8 (62)
Age, years	64 (61–71)
Height, cm	177 (174–186)
Weight, kg	84 (74–95)
BMI, kg/m^2	27 (24–28)
Reason for ICU admission, *n* (%)	
Medical	9 (70)
Surgical	4 (30)
Reason for ARDS, *n* (%)	
Sepsis	8 (62)
Pneumonia	2 (15)
Trauma	3 (23)
APACHE II score	28 (24–31)
ARDS severity, *n* (%)	
Moderate	1 (8)
Severe	12 (92)

Data are median (IQR) or *N*/total (%)

BMI body mass index, *ARDS* acute respiratory distress syndrome, *APACHE* Acute Physiology and Chronic Health Evaluation

was <15 cmH$_2$O in 9 out of 13 vs. 10 out of 13 patients with conventional ventilation (at 81% vs. 87% of all time points). While median V_T increased in 8 out of 13 patients, median RR decreased in 12 out of 13 patients (Additional file 1: Fig. S1) overall leading to a lower minute volume with closed-loop ventilation. V_T increased mainly with closed-loop ventilation when a patient had a higher C_{RS} (Additional file 1: Figs. S2 and S3). A higher V_T did not lead to a higher ΔP_{TP} with closed-loop ventilation at most time points (Fig. 3) and P_{TP} was lower with closed-loop ventilation. There were no differences in median PEEP (Additional file 1: Fig. S4), FiO$_2$ and C_{RS}. Individual effects of the ventilation modes over time on ΔP_{TP}, PEEP, V_T and RR are shown in Additional file 1: Figs. S5–S8.

Gas exchange was not affected, with no differences in PaO$_2$ and PaCO$_2$ between the two cross-over phases (Table 2). EtCO$_2$ was higher with closed-loop ventilation, but SpO$_2$ was not different. Pairwise comparisons of ventilatory parameters at the individual time points with the Bonferroni adjustment showed that they were not significant at all time points (Additional file 1: Table S1 and Figs. S9–S13).

Post hoc analyses

While MP$_{RS}$ was not different between closed-loop ventilation and conventional ventilation, median MP$_{TP}$ was lower with closed-loop ventilation (Table 2, Figs. 2 and 3). The linear mixed model analysis did not change the findings of the primary analysis, meaning that ΔP_{TP} was lower with closed-loop ventilation and time as well as the interaction between ventilation and time of treatment was not significant. Thus, it is likely that the ventilation mode had a direct effect, which did not increase over time. The model is specified in Additional file 1: Table S2.

Buiteman-Kruizinga *et al. Intensive Care Medicine Experimental* (2023) 11:42

Page 8 of 13

Table 2 Ventilation parameters

|	INTELLiVENT-ASV	Conventional ventilation	*P* value
Primary endpoint			
ΔP_{TP} (cmH$_2$O)	7.0 (5.0–10.0)	10.0 (8.0–11.0)	0.0002
Secondary endpoint			
ΔP_{RS} (cmH$_2$O)	12.8 (12.0–15.0)	13.2 (12.0–15.0)	0.35
Pplat (cmH$_2$O)	24.0 (24.0–25.0)	25.0 (24.0–26.0)	0.055
PEEP (cmH$_2$O)	12.0 (10.0–12.0)	12.0 (9.0–12.0)	0.55
P_{TP} inspiratory	18.0 (17.0–20.0)	20.0 (19.0–23.0)	0.0002
V_T (mL)	498 (462–517)	453 (419–490)	0.003
V_T (mL/kg PBW)	6.9 (6.4–7.2)	6.3 (5.8–6.8)	0.002
RR (breaths/min)	20 (18–21)	23 (21–23)	< 0.001
Min. Vol (L/min)	9.8 (8.9–10.5)	10.1 (9.2–11.1)	0.03
C_{RS} (mL/cmH$_2$O)	34.0 (31.0–41.0)	34.0 (30.0–39.0)	0.11
C_L (mL/cmH$_2$O)	26.1 (23.5–29.7)	21.8 (19.6–24.3)	0.00027
C_{CW} (mL/cmH$_2$O)	83.5 (67.8–96.1)	124.5 (99.6–186.5)	0.0003
E_L (cmH$_2$O/L)	15.2 (11.3–19.1)	22.5 (16.7–26.5)	< 0.001
MP_{TP} (J/min)	14.1 (12.7–15.6)	15.7 (14.2–17.4)	0.0006
MP_{RS} (J/min)	17.1 (15.7–18.9)	17.7 (15.6–19.4)	0.51
FiO$_2$ (%)	0.63 (0.50–0.70)	0.60 (0.50–0.67)	0.06
SpO$_2$ (%)	94 (93–96)	96 (93–96)	0.07
etCO$_2$ (kPa)	6.3 (5.3–6.7)	6.1 (5.8–6.7)	0.001
VR	1.9 (1.7–2.5)	2.3 (2.0–2.7)	0.095
Blood gas variables			
pH	7.31 (7.28–7.34)	7.32 (7.29–7.34)	0.79
pCO$_2$ (kPa)	7.9 (6.7–8.4)	7.7 (7.1–8.0)	0.53
pO$_2$ (kPa)	8.7 (7.9–9.6)	8.9 (8.1–9.9)	0.62
Bic (mmol/L)	20.0 (18.0–22.0)	21.0 (18.0–22.0)	0.43
Arterial sat. (%)	94 (93–96)	96 (93–96)	0.17

Data are median (IQR)

ΔP_{TP}: transpulmonary driving pressure; ΔP_{RS}: driving pressure of the respiratory system; MP: mechanical power; MP_{TP}: transpulmonary mechanical power; Pplat: plateau pressure; P_{TP} inspiratory: inspiratory transpulmonary pressure; V_T: tidal volume; PBW: predicted body weight; cmH$_2$O: centimeters of water; RR: respiratory rate; C_{RS}: compliance of the respiratory system; C_L: compliance of the lung; C_{CW}: compliance of the chest wall; E_L: lung elastance; Vol: minute volume; FiO$_2$: fraction of inspired oxygen; SpO$_2$: pulse oximetry; etCO$_2$: end-tidal carbon dioxide; VR: ventilatory ratio; kPa: kilopascal; Bic: bicarbonate

Discussion

The findings of this physiological randomized cross-over clinical trial in a limited number of patients with moderate-to-severe ARDS can be summarized as follows: (i) compared to conventional ventilation, INTELLiVENT-ASV, a closed-loop ventilation mode that targets the lowest work and force of breathing, reduces ΔP_{TP} and P_{TP}; (ii) increases V_T; and (iii) reduces RR.

The study has several strengths. First, by using a cross-over design we were able to compare ventilation parameters between conventional with closed-loop ventilation wherein each patient served as his or her own control. This increased the statistical power of this relatively small study. Next, the study protocol was simple and strictly followed in all patients. All doctors and nurses were well-trained and experienced in applying lung-protective ventilation, skilled in using the closed-loop mode, and qualified in using the esophageal balloon catheter. Given that the cross-over periods lasted only 4 h,
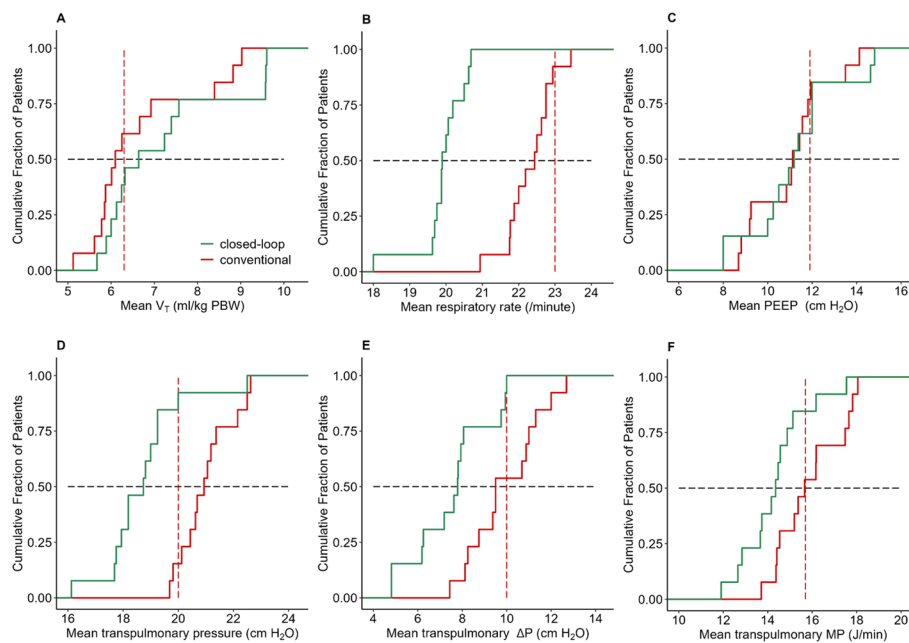
Fig. 2 Cumulative frequency distribution of **A** V_T, **B** RR, **C** PEEP, **D** inspiratory transpulmonary pressure, **E** transpulmonary ΔP and **F** transpulmonary MP. The plots show the mean variables with closed-loop ventilation and conventional ventilation. Vertical dotted lines represent the median value with conventional ventilation. Horizontal dotted lines show the respective proportion of patients reaching each cutoff
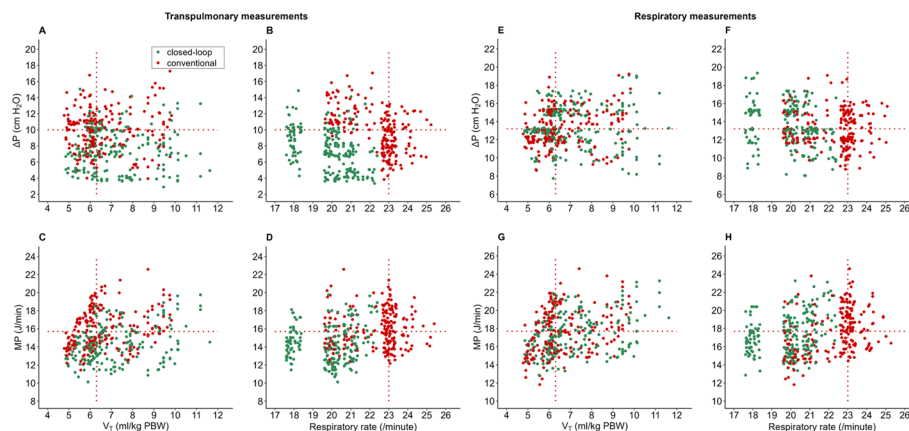
Fig. 3 Scatterplots of transpulmonary measurements of the relationship of **A** V_T vs ΔP_{TP}, **B** RR vs ΔP_{TP}, **C** V_T vs MP_{TP} and **D** RR vs MP_{TP}, and respiratory system measurements of **E** V_T vs ΔP_{RS}, **F** RR vs ΔP_{RS}, **G** V_T vs MP_{RS} and **H** RR vs MP_{RS}, with closed-loop ventilation and conventional ventilation. Each time point of the individual patient was characterized by a single data point. Horizontal and vertical lines represent the median for the corresponding value with conventional ventilation. This figure visualizes the relation between the variables, and for instance shows that higher V_T does not necessarily translates in a higher ΔP_{TP} (**A**) or MP_{TP} (**C**) in individual patients. The horizontal and vertical lines based on median values in the current study create quadrants that could be used for interpretation of whether a certain combination is completely, or partially within safe zones of ventilation

changes in ventilator parameters are most likely the result of the switch to the alternative ventilation mode, rather than changes in the patients' lung conditions. Finally, we strictly followed a predefined statistical analysis plan, written before cleaning and closing of the database.

To our best knowledge, is this the first study that compares ΔP_{TP} between closed-loop and conventional ventilation. Using transpulmonary pressures, instead of respiratory system pressures, allowed us to reduce the 'noise' that comes from possible increases in chest wall elastance [27] and airway resistance. In other words, this approach allowed us to determine better the effects of this closed-loop mode designed to target the lowest work and force of breathing on lung stress [3, 18, 28]. A lower ΔP_{TP} suggests that ventilation is provided in a more lung-protective way, possibly reducing the risks for or extend of ventilator-induced lung injury (VILI) [29].

The findings of our study extend current knowledge regarding the tested closed-loop ventilation mode. While previous studies showed that this closed-loop ventilation mode results in a lower ΔP_{RS} and ΔP_{TP}, thus far only ΔP_{RS} has been compared directly with conventional ventilation [11–13, 24]. The results of our study show that a switch to closed-loop ventilation results in fast changes in ventilator settings in a relatively short period. Of note, we studied patients in the early phase of ARDS. Usually, this is a period during which many interventions take place, meaning that there is little time for setting the ventilator properly. Closed-loop ventilation modes can support health care providers in providing lung-protective ventilation in this often-hectic phase.

The finding that V_T size increases while ΔP decreases is in line with the findings of previous investigations. Indeed, we and others recently showed similar changes when switching the ventilator from conventional ventilation to closed-loop ventilation [12, 13, 30, 31]. The algorithms underneath INTELLiVENT-ASV target the lowest work of breathing [9] and the lowest force of breathing [10]. The first leads to the 'best' combination for RR and V_T, based on the expiratory time constant (RC_{exp}): the RR is gradually reduced while the inspiratory pressure (Pinsp) is titrated up to achieve a minute volume that fits the patient best. It may seem surprising then to see that while V_T increases, ΔP_{TP} decreases. This apparent contradiction may be explained as follows. First, in our study, ΔP_{TP} decreases and V_T increases, because pulmonary compliance increased with closed-loop ventilation, meaning that lung mechanics improved. This physiological mechanism could be explained by the fact that PEEP is automatically adjusted with closed-loop ventilation. There was no difference in median PEEP, but the adjustments over time we visualize in individual patients could have led to recruitment or less overdistension, resulting in the best possible compliance and a lower ΔP_{TP}. Second, one algorithm of INTELLiVENT-ASV allows for permissive hypercapnia, meaning that at higher pressures, the system chooses to target a higher end-tidal CO_2. Consequently, the minute volume is reduced, and this goal is mainly reached through a reduction in RR, as shown in our study. This may effect ΔP as with a lower RR there is more time for gas exchange, and preventing wasted ventilation in patients with ARDS that have increased physiological dead space [32], as reflected by the lower ventilatory ratio in our study during closed-loop ventilation. Also, a lower RR can decrease stress and strain on lung tissue [33], because it is important to consider the level of stress and strain delivered with each breath (reflected by the ΔP), but also how often this is repeated (reflected by the

RR). Some preclinical studies indicate that lowering the respiratory rate can reduce the risk of VILI [34–36].

Important to mention is that in 2 out of 13 patients V_T was >8 mL/kg PBW with closed-loop ventilation. Of note, this was only the case in patients that were also receiving a V_T >8 mL/kg PBW with conventional ventilation. Nevertheless, this is above the generally accepted safety limits for V_T [37]. Interestingly, in these patients the ΔP remained low at all times. This may be explained that ventilatory strategies with a lower V_T and higher RR may only be beneficial for patients with very low C_{RS} [38]. In contrast to patients with a not so low C_{RS}, where a higher V_T, with the benefit of a lower RR, can be acceptable as long as ΔP remains below < 15 cmH$_2$O [39–41].

The post hoc analysis showed a decrease in MP$_{TP}$. MP is the energy transferred from the ventilator to the respiratory system, and together with ΔP reflect the 'intensity' of ventilation. Not only the ΔP, but also the MP has been shown to have associations with outcomes [4, 5, 25, 42]. Taken together, the findings of our study suggest that the closed-loop mode of interest reduces the intensity of ventilation in most patients, with respect to all factors that have associations with worse outcomes—V_T, plateau pressure, ΔP and RR. This is also reflected by the summary value, i.e., MP.

This study has limitations. Blinding of the doctors and nurses taking care of the patients was not possible because of the nature of the intervention. The analysis of collected data, though, was done by an investigator that was blinded for the randomization phase. Second, the study was stopped early, because of an increased use of ELS in patients with ARDS at the study site. However, the predefined sample-size was reached for the cross-over part of the study. As this was a single-center study, we may not generalize its findings. We stress, however, that the team of doctors and nurses were experienced in applying lung-protective ventilation, which may not be the case everywhere. From the individual data we learned that not all patients respond in the same way to a switch between the two modes—individual patient responses need further attention in future studies. Last but not least, it is attractive to think and perhaps even plausible that a decrease in ΔP translates into clinical benefits, but this remains to be proven in future studies.

Conclusion

In patients in the early phase of moderate-to-severe ARDS, a closed-loop mode that targets the lowest work and force of breathing decreases the transpulmonary ΔP in this small physiological study. Use of this mode also lowered RR, and MP. Future studies remain needed to determine if these changes provide clinical benefits.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40635-023-00527-1.

Additional file 1: Table S1. List of significant pairwise comparisons per time point, significance was determined at a *P* value < 0.003. **Table S2.** Specification of the generalized linear mixed model analysis. **Figure S1.** Line plots showing the mean changes and individual changes over time of transpulmonary ΔP, V_T and RR during the two study blocks of the two ventilation modes in the study. **Figure S2.** C_{RS} vs. V_T between closed-loop ventilation and conventional ventilation, and transpulmonary ΔP vs. V_T between closed-loop ventilation and conventional ventilation. A negative value means that the parameter decreased with closed-loop ventilation, and a higher value means that the parameter increased with closed-loop ventilation. All dots represent the mean value of an individual patient. **Figure S3.** Scatterplots of C_{RS} vs. V_T and transpulmonary ΔP vs. V_T with closed-loop ventilation and conventional ventilation. Each dot was characterized by a single data point. **Figure S4.** Showing individual patient data of the effect of the

change of the ventilation mode on PEEP setting. **Figure S5.** Showing transpulmonary ΔP per patient during every time point, with closed-loop ventilation and conventional ventilation. The head with number represents the corresponding patient, the *x*-axis represent the 16 time points per block. **Figure S6.** Showing PEEP per patient during every time point, with closed-loop ventilation and conventional ventilation. The head with number represents the corresponding patient, the *x*-axis represent the 16 time points per block. **Figure S7.** Showing the tidal volumeper patient during every time point, with closed-loop ventilation and conventional ventilation. The head with number represents the corresponding patient, the *x*-axis represent the 16 time points per block. **Figure S8.** Showing the respiratory rateper patient during every time point, with closed-loop ventilation and conventional ventilation. The head with number represents the corresponding patient, the *x*-axis represent the 16 time points per block. **Figure S9.** Violin plot of pairwise comparisons at individual time points of ΔP. **Figure S10.** Violin plot of pairwise comparisons at individual time points of transpulmonary ΔP. **Figure S11.** Violin plot of pairwise comparisons at individual time points of RR. **Figure S12.** Violin plot of pairwise comparisons at individual time points of MP. **Figure S13.** Violin plot of pairwise comparisons at individual time points of transpulmonary MP.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the local Institutional Review Board of the Academic Medical Center, Amsterdam (April 13, 2017; 2016_349#B2017211). Written informed consent was obtained from a legal representative of the patient before inclusion and randomization. This study was conducted in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
LBK received fees from Hamilton Medical for lecturing. MJS was a team leader of Research and New Technologies at Hamilton Medical from January 2022 till January 2023. Of note, the study was designed, performed and finalized before one of the authors (MJS) accepted this time-limited part-time position at Hamilton Medical AG, Bonaduz, Switzerland, before submission of this manuscript. The other authors declare no conflicts of interest.

References
1. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA et al (2015) Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 372(8):747–755
2. van Meenen DMP, Serpa Neto A, Paulus F, Merkies C, Schouten LR, Bos LD et al (2020) The predictive validity for mortality of the driving pressure and the mechanical power of ventilation. Intensive Care Med Exp 8(Suppl 1):60
3. Tonetti T, Vasques F, Rapetti F, Maiolo G, Collino F, Romitti F et al (2017) Driving pressure and mechanical power: new targets for VILI prevention. Ann Transl Med 5(14):286
4. Guérin C, Papazian L, Reignier J, Ayzac L, Loundou A, Forel JM (2016) Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials. Crit Care 20(1):384
5. Urner M, Jüni P, Hansen B, Wettstein MS, Ferguson ND, Fan E (2020) Time-varying intensity of mechanical ventilation and mortality in patients with acute respiratory failure: a registry-based, prospective cohort study. Lancet Respir Med 8(9):905–913
6. Neto AS, Hemmes SN, Barbas CS, Beiderlinden M, Fernandez-Bustamante A, Futier E et al (2016) Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data. Lancet Respir Med 4(4):272–280
7. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A et al (2016) Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 315(8):788–800
8. Buiteman-Kruizinga LA, Serpa Neto A, Schultz MJ (2022) Automation to improve lung protection. Intensive Care Med 48(7):943–946
9. Otis AB, Fenn WO, Rahn H (1950) Mechanics of breathing in man. J Appl Physiol 2(11):592–607

10. Mead J (1963) The control of respiratory frequency. Ann N Y Acad Sci 109:724–729
11. De Bie AJR, Neto AS, van Meenen DM, Bouwman AR, Roos AN, Lameijer JR et al (2020) Fully automated postoperative ventilation in cardiac surgery patients: a randomised clinical trial. Br J Anaesth 125(5):739–749
12. Buiteman-Kruizinga LA, Mkadmi HE, Serpa Neto A, Kruizinga MD, Botta M, Schultz MJ et al (2021) Effect of INTELLiVENT-ASV versus conventional ventilation on ventilation intensity in patients with COVID-19 ARDS—an observational study. J Clin Med 10(22):5409
13. Wendel Garcia PD, Hofmaenner DA, Brugger SD, Acevedo CT, Bartussek J, Camen G et al (2021) Closed-loop versus conventional mechanical ventilation in COVID-19 ARDS. J Intensive Care Med 36(10):1184–1193
14. Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F et al (2008) Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. Am J Respir Crit Care Med 178(4):346–355
15. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E et al (2012) Acute respiratory distress syndrome: the Berlin definition. JAMA 307(23):2526–2533
16. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH et al (2014) The application of esophageal pressure measurement in patients with respiratory failure. Am J Respir Crit Care Med 189(5):520–531
17. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M et al (2004) Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351(4):327–336
18. Chiumello D, Carlesso E, Brioni M, Cressoni M (2016) Airway driving pressure and lung stress in ARDS patients. Crit Care 20:276
19. Bugedo G, Retamal J, Bruhn A (2017) Driving pressure: a marker of severity, a safety limit, or a goal for mechanical ventilation? Crit Care 21(1):199
20. Umbrello M, Chiumello D (2018) Interpretation of the transpulmonary pressure in the critically ill patient. Ann Transl Med 6(19):383
21. Geboers DG, de Beer FM, Tuip-de Boer AM, van der Poll T, Horn J, Cremer OL et al (2015) Plasma suPAR as a prognostic biological marker for ICU mortality in ARDS patients. Intensive Care Med 41(7):1281–1290
22. Arnal JM, Saoli MS, Novotni D, Garnero A (2016) Driving pressure automatically selected by INTELLiVENT-ASV in ICU patients. Abstract ESICM
23. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O et al (2016) Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 42(10):1567–1575
24. Arnal JM, Saoli M, Garnero A (2020) Airway and transpulmonary driving pressures and mechanical powers selected by INTELLiVENT-ASV in passive, mechanically ventilated ICU patients. Heart Lung 49(4):427–434
25. Coppola S, Caccioppola A, Froio S, Formenti P, De Giorgis V, Galanti V et al (2020) Effect of mechanical power on intensive care mortality in ARDS patients. Crit Care 24(1):246
26. van Buuren S (2018) Flexible imputation of missing data, 2nd edn. Chapman and Hall/CRC, New York, p 444
27. Cortes-Puentes GA, Keenan JC, Adams AB, Parker ED, Dries DJ, Marini JJ (2015) Impact of chest wall modifications and lung injury on the correspondence between airway and transpulmonary driving pressures. Crit Care Med 43(8):e287–e295
28. Pistillo N, Fariña O (2018) Driving airway and transpulmonary pressure are correlated to VILI determinants during controlled ventilation. Intensive Care Med 44(5):674–675
29. Silva PL, Gama de Abreu M (2018) Regional distribution of transpulmonary pressure. Ann Transl Med 6(19):385
30. Baedorf Kassis EN, Bastos AB, Schaefer MS, Capers K, Hoenig B, Banner-Goodspeed V et al (2022) Adaptive support ventilation and lung-protective ventilation in ARDS. Respir Care 67(12):1542–1550
31. Buiteman-Kruizinga LA, Schultz MJ (2023) The (mechanical) power of (automated) ventilation. Respir Care 68(4):556
32. Robertson HT (2015) Dead space: the physiology of wasted ventilation. Eur Respir J 45(6):1704–1716
33. Rezoagli E, Laffey JG, Bellani G (2022) Monitoring lung injury severity and ventilation intensity during mechanical ventilation. Semin Respir Crit Care Med 43(3):346–368
34. Hotchkiss JR Jr, Blanch L, Murias G et al (2000) Effects of decreased respiratory frequency on ventilator-induced lung injury. Am J Respir Crit Care Med 161:463–468
35. Protti A, Maraffi T, Milesi M, Votta E, Santini A, Pugni P et al (2016) Role of strain rate in the pathogenesis of ventilator-induced lung edema. Crit Care Med 44(9):e838–e845
36. Akoumianaki E, Vaporidi K, Georgopoulos D (2019) The injurious effects of elevated or nonelevated respiratory rate during mechanical ventilation. Am J Respir Crit Care Med 199(2):149–157
37. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342(18):1301–1308
38. Goligher EC, Costa ELV, Yarnell CJ, Brochard LJ, Stewart TE, Tomlinson G et al (2021) Effect of lowering Vt on mortality in acute respiratory distress syndrome varies with respiratory system elastance. Am J Respir Crit Care Med 203(11):1378–1385
39. Costa ELV, Slutsky AS, Brochard LJ, Brower R, Serpa-Neto A, Cavalcanti AB et al (2021) Ventilatory variables and mechanical power in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 204(3):303–311
40. Georgopoulos D, Xirouchaki N, Tzanakis N, Younes M (2016) Driving pressure during assisted mechanical ventilation: is it controlled by patient brain? Respir Physiol Neurobiol 228:69–75
41. Vaporidi K, Psarologakis C, Proklou A, Pediaditis E, Akoumianaki E, Koutsiana E et al (2019) Driving pressure during proportional assist ventilation: an observational study. Ann Intensive Care 9(1):1
42. Serpa Neto A, Deliberato RO, Johnson AEW, Bos LD, Amorim P, Pereira SM et al (2018) Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. Intensive Care Med 44(11):1914–1922

Publisher's Note