COVER PAGE

Full title:

The Full Closed Loop Ventilation Mode INTELLiVENT-ASV: User-friendly and Effective Mechanical Ventilation in High Risk Postoperative Patient on the Intensive Care Unit.

Brief title:

Postoperative INTELLiVENT-ASV Ventilation (POSITiVE).

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Statistical analysis plan and protocol update.

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Statistical analysis plan and protocol update of the POSiTIVE study.

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ABSTRACT

BACKGROUND: INTELLiVENT-ASV is a fully closed ventilation mode that can automatically adjust ventilation settings in both passive and active ventilated patients. Current literature shows that this mode is safe to use in patients admitted on the intensive care unit. Compared to conventional modes of ventilation, INTELLiVENT-ASV may be even more effective in terms of lung protective ventilation compared to conventional mechanical ventilation, while being more user-friendly, since the ventilator regulates the ventilation automatically. However, randomized trials testing these hypotheses in postoperative high-risk patients are scarce.

METHODS/DESIGN: The POSiTIVE trial was a prospective randomized controlled trial that compared conventional ventilation (continuous mandatory or pressure controlled ventilation with pressure support) with INTELLiVENT-ASV in postoperative high-risk cardiac surgery patients. The primary outcome was to compare the percentage of mechanical ventilation time within the unacceptable zone between both groups. Secondary endpoints included comparing the percentage of mechanical ventilation time and breathings in the optimal and acceptable zones, time until extubation, number of successful extubations (without reintubation ≤48hours), the incidence of complications including pneumonia, atelectasis and pneumothorax, user-acceptance, number of ventilator alarms and interactions, and the course of mechanical ventilation parameters like tidal volume based on ideal body weight, driving pressure and mechanical power.

DISCUSSION: Enrollment of patients was complete on April 19, 2018. The 30-day follow–up for the last included patient was on the end of May, 2018.

Thereafter, the database will be cleaned and locked, which is expected on October 1, 2018.

TRIAL REGISTRATION: The trial is registered at www.clinicaltrials.gov under reference number NCT03180203 on 08 June 2017.

KEYWORDS: Mechanical ventilation, protective ventilation, intensive care unit, INTELLiVENT-ASV ventilation mode, Fully closed loop ventilation, postoperative ventilation.

INTRODUCTION

The POSiTIVE trial is a randomized clinical trial comparing two strategies of ventilation, the conventional ventilation and the full closed loop mode, in postoperative high-risk cardiac surgery patients admitted in the intensive care unit (ICU) [1]. The primary objective of this trial is to determine whether the percentage of ventilation time within the unacceptable zone is lower when patients are ventilated with INTELLiVENT-ASV compared to conventional ventilation (the combination of continuous mandatory or pressure controlled ventilation with pressure support) in the first three hours of ventilation or until extubation. Enrollment of patients started on the May 20, 2017, and completed on April 19, 2018. Follow–up of the last patient completed on the end of May, 2018. Since data was collected in a breath by breath way, data collection and cleaning is expected to be complete within 6 months. Thereafter the database will be finally closed.

Based on recommendations of the International Conference on Harmonization of Good Clinical Practice (ICH–GCP) a pre–specified detailed statistical analysis plan is conceived to prevent outcome reporting bias and data–driven analysis results [2]. The present study update and statistical analysis plan are drafted without knowledge of outcome data.

METHODS

Design

This is a single center, randomized, controlled, pragmatic trial comparing two strategies of ventilation, the conventional ventilation and the full closed loop mode, in postoperative high-risk cardiac surgery patients admitted in the intensive care unit (ICU). The trial was conducted in the ICU of the Catharina hospital in The Netherlands, a tertiary teaching hospital, specialized in cardiac surgery. The trial protocol was registered in ClinicalTrials.gov (NCT03180203) and was approved by the Medical Research Ethics Committees United (MEC-U), Nieuwegein, The Netherlands, under reference number R16.054.

Eligibility of the patients

Consecutive patients that would be admitted to receive cardiac surgery were screened for eligibility. Patients received information of the trial on the day they had their preoperative anesthesia assessment and consent was obtained the day before surgery if the patient fulfilled the inclusion and exclusion criteria. Informed consent was asked from the patient in all cases before surgery. The patient was excluded if after randomization the consent was withdrew.

Inclusion and exclusion criteria

Inclusion criteria were an age >18 years old, elective cardiac surgery which included bypass, valve and ascending aortic surgery, a body mass index of < 35 kg/m^2, and postoperative treatment with mechanical ventilation on a high or intensive care unit. Exclusion criteria were, postoperative ARDS according to the Berlin definition [3], postoperative need for extracorporeal membrane

oxygenation, postoperative admission on the Post Anesthesia Care Unit (which was preoperatively determined by the anesthiologist), a medical history containing pneumonectomy, lobectomy or chronic obstructive lung disease GOLD 3 or 4 classification, and patients participating in another postoperative study on the intensive care.

Randomization and blinding.

A simple randomization method was used to randomly allocate patients in a 1:1 ratio to the conventional ventilation group or the INTELLiVENT-ASV group. Randomization was performed using the list randomizer on the website www.random.org. Randomization and allocation was performed immediately after the informed consent form was signed and the allocation of the patient was known only at the moment of the randomization. A hardcopy of the randomization outcome was printed with timestamp, signed and archived.

The physician and the team caring for the patients were not blinded. The researcher performing the data analyses, the radiologist that evaluates the postoperative chest X-rays, and the statistician performing the data analyses will be blinded.

The ventilation strategies

Patients randomized to the conventional ventilation group received a continuous mandatory volume or pressure controlled ventilation, if they were not breathing spontaneously, immediately after the admission in the ICU. Based on physician criterion ventilator settings were set by the anesthesiologist in consultation with the intensivist and ICU nurse on duty during the postoperative handover.

Pressure support mode was selected if patients were breathing spontaneously during handover. After the handover the ICU nurse or ICU physician could adjust ventilator settings during mechanical ventilation. If needed the ICU nurse could always consult the ICU physicians on duty. It was not possible to extubate the patient without consulting the ICU physician on duty, who made the final call to extubate. Spontaneous breathing trials (SBT) were not applied during the first three hours of mechanical ventilation. The patient was extubated without a SBT if the physicians decided that the patient could be extubated within the first three hours of mechanical ventilation. Postoperative ventilation and weaning was performed based on local hospital protocols that targets lung protective ventilations with a target tidal volume of 6ml/kg of PBW. The standard operating procedure is described in appendix 1.The predicted body weight (PBW) that is used in etable 3 is calculated according to a previously used formula [5]:

- 50 + 0.91 x (centimeters of height – 152.4) for male; and
- 45.5 + 0.91 x (centimeters of height – 152.4) for females.

Patients randomized to the INTELLiVENT-ASV group received this mode of ventilation immediately after the admission in the ICU. Quickwean was immediately activated at that time, but the SBT mode was switch off for the first three hours of mechanical ventilation. It was not possible to extubate the patient without consulting the ICU physician on duty, who made the final call to extubate. Spontaneous breathing trials (SBT) were not applied during the first three hours of mechanical ventilation. The patient was extubated without a SBT if the physicians decided that the patient could be extubated within the first three hours of mechanical ventilation. After the first three hours of ventilation the SBT function

of INTELLiVENT-ASV was initiated and the patient could be extubated if the patient had a successful SBT of at least 10 minutes with a consultation of the ICU physician on duty. The standard operating procedure is described in appendix 2.

In both arms it was possible to deviate from protocol if the ICU physician deemed it necessary for the safety of the patient. In these cases the patient could be switched to the not allocated mode.

In both arms the same alarm settings were used, which were: 1) pressure alarm ≥35 cmH2O; 2) expiratory minute volume alarm ≤3.0 and ≥15.0 L/min; 3) respiratory rate alarm ≥35 breaths per min; 4) tidal volume alarm ≥ 900 ml; 5) apnea time alarm ≥30 seconds; 6) EtCO2 alarm ≤30 and ≥60mmHg; and 7) SpO2 alarm ≤90%.

Outcomes

Primary outcome:

1. Percentage of time (during at least 30 seconds) in the unacceptable zone according to the total postoperative ventilation time on the ICU during the first three hours of ventilation or until extubation, if extubated earlier.

Secondary outcomes:

1. Percentage of time (during at least 30 seconds) in the optimal and acceptable zone according to the total postoperative ventilation time during the first three hours of ventilation or until extubation, if extubated earlier.
2. Percentage of breaths in the optimal, acceptable and unacceptable zone according to the total number of recorded breaths during the first three hours of ventilation or until extubation, if extubated earlier.

3. Percentage of time (during at least 30 seconds) in the optimal, acceptable and unacceptable zone according to the total number of recorded time.
4. Percentage of breaths in the optimal, acceptable and unacceptable zone according to the total number of recorded breaths.
5. Ventilator variables and vital signs will be reported after each half an hour from ICU admission until spontaneous breathing (>5 consecutive spontaneous breaths) or the first three hours of mechanical controlled ventilation. Ventilator variables include the manually measured tidal volume, driving pressure and mechanical power. Driving pressure will be calculated by extracting the PEEP after >5 seconds of an expiratory hold from the plateau pressure level after >5 seconds of an inspiratory hold. Both this recorded PEEP and plateau pressure were used with other manually recorded parameters to calculate the mechanical power: $Power_{rs}=RR\cdot\{\Delta V^2*[(0.5*EL_{rs})+(RR*((1+I:E)/(60*I:E))*R_{aw}))]+\Delta V*PEEP\}$.[6]
   Vital signs include also $EtCO_2$: $PaCO_2$ and PaO_2: FIO_2 ratio that were conducted at admission and after approximately an hour of ventilation.
6. The number patients extubated in the first six, twelve and twenty-four hours after surgery without a reintubation or non-invasive ventilation ≤48 hours after extubation for respiratory insufficiency (a successful extubation).
7. Ventilation time considered as the time from intubation during surgery until first and first successful extubation adjusted by the duration of surgery.
8. Weaning duration considered as the time from stopping intravenous sedativesand a rectal temperature of ≥35.5°C since admission on the ICU until successful extubation.

9. The time from intubation during surgery until spontaneous breathing (at least ≥5 consecutive spontaneous breaths) adjusted by the duration of surgery.
10. The time from stopping intravenous sedatives with a rectal temperature of ≥35.5°C during admission on the ICU until spontaneous breathing (at least ≥5 consecutive spontaneous breaths).
11. The total number of alarms and interventions per hour within the first 3 hours or until extubation.
12. The total number of alarms and interventions per hour according to the total registered ventilation time.
13. ICU mortality
14. 30 day mortality
15. The number of ICU readmissions during the first 72 hours after ICU discharge.
16. ICU length of stay.
17. The number of agitated moment, established by the nurse at the bedside.
18. The number of bolus administration of sedatives and analgesics.
19. The number of patients with postoperative pulmonary complications (like pneumonia, pneumothorax, atelectasis on the X-ray within the first 72 hours after surgery).
20. The percentage of breaths that the SpO2 measurements were <85% according to the total number of recorded breaths (when the measured SpO2 had a quality index of >50%).
21. The percentage of breaths that the EtCO2 and SpO2 measurements were missing or of a quality of <51%.

22. The median acceptance score (1-10) of the nurse. The answers of the whole survey will be published as supplementary data.
23. During this study the pressure, volume, flow and $EtCO_2$ wave patterns were recorded to analyze and detect patient-ventilator asynchronies. Currently new algorithms are developed to analyze the wave patterns in an objective and reliable manner. Based on these algorithms the research group will try to compare the number and the type of asynchronies during mechanical controlled and supportive ventilation in both groups. These outcomes will be reported in another manuscript than the outcomes described above.

Study organization

The steering committee was composed of the principal investigator that was also the local coordinating investigator and five experts in ventilator support in critically ill patients all contribute to the design and revisions of the original study protocol and the statistical analysis plan. The local coordinating investigator was responsible for administrative management and for collection and management. The local coordinating investigator was supported by six local investigators to cover in duties when the local coordinating investigator could not record the data. All local investigators were registered in the delegation log. The study was conducted according to the ICH–GCP guidelines, to guaranty integrity of data collection and to ensure timely completion of the case report forms at the bedside completed by the ventilator users.

Data collection

During the study paper case report forms and a paper survey for user-acceptance were used at the bedside. All paper forms were archived. Patient characteristics and follow-up data were extracted from the electronic medical record. All collected data were registered in digital databases, Excel (© 2010 Microsoft Corporation, Redmond, Washington) and SPSS (© version 25, IBM Corp., Armonk, NY, USA). A datalogger (© 2013 HAMILTON MEDICAL AG, Switzerland) connected to the mechanical ventilator was used to obtain the objective "breath-by-breath" data concerning ventilation parameters. Local investigators entered other data on paper which was archived and this data was registered in the previous mentioned digital databases by the local coordinating investigator. Electronic files were archived in the Catharina Hospital based server in a secure and controlled environment to maintain confidentiality. Electronic documents were controlled with password protection according to best practices.

Data management

An independent monitor of the Catharina Hospital evaluated the study. The monitoring comprised controlling presence and completeness of the research dossier and the informed consent forms, and source data checks were performed. The monitor decided that data collection and management was according to the ICH–GCP guidelines and that the integrity of data collection and management was guaranteed.

Data monitoring board and safety analyses

The Medical Research Ethics Committees United and local hospital board decided that a data monitoring board (DSMB) and safety analyses were not

required since all used ventilation modes in the study were already common practice on the studied ICU.

Cleaning and locking of the database

The ventilatory variables will be extracted from the datalogger output files and transferred to the databases that will be exported for statistical analysis. After that, these study databases will be locked and exported for statistical analysis to the Academic Medical Center, Amsterdam, The Netherlands. The results of this analyses will be documented in a comprehensive database. At this stage, this last database will be locked as soon as all data are entered and all discrepant or missing data are resolved – or if all efforts are employed and remaining issues cannot be fixed. At this step, the data will be reviewed before database locking. At this stage, permission for access to the database will be removed for all investigators, and the database will be archived.

Missing data

No or minimal missing for the primary and secondary outcomes are anticipated, except for the quality and number of SpO_2 measurement in the datalogger. These measurement are assessed with fingertip pulse oximeter that sometimes cannot assess a value or the quality of the assessment is not sufficient. Breaths with missing SpO_2 or a quality of the assessment of < 51% will be excluded from the analyses of the primary and secondary outcomes where this measurements are necessary.

Sample size

A power analysis was performed using G*Power (version 3.1.9.2.; Franz Faul, Universitiet Kiel, Duitsland). Based on this analysis the trial was designed to enroll at least 196 patients in total. This number of patients was expected to be sufficient to detect a reduced ventilation time of 14.0 minutes in the unacceptable zone in the INTELLiVENT-ASV group considering a common standard deviation of 10.0 minutes [4], a type I error of 5%, 95% of power, similar allocation of subjects to each group and corrected for dropouts.

Predefined statistical analysis plan

There were no major adjustments from the preliminary analysis plan, as reported previously in the online accessible protocol [1]. In accordance, all statistical analyses will be conducted according to an intention–to–treat principle, considering all patients in the treatment groups to which they were randomly assigned.

Visual inspection of histograms and D'Agostino–Pearson's normality tests will be used to assess continuous distribution of the data. For the conventional ventilation and INTELLiVENT-ASV arms, the baseline characteristics will be expressed as counts and percentages, means and standard deviations (SD), or medians and interquartile ranges (IQR) whenever appropriate. Hypothesis tests will be two–sided with a significance level of 5%. We will not adjust *P*–values for multiple comparisons. Analyses will be performed using the R (R Core Team, 2016, Vienna, Austria) program.

Trial profile: Patient flows will be presented in a CONSORT flowchart (Figure 1).

Baseline comparisons: Patient's baseline characteristics will be presented by study arm (eTable 2).

Adherence to study interventions and, ventilator variables and vital signs: Ventilatory variables and vital signs will be reported from ICU admission until extubation or up to the first 72hours of recorded mechanical ventilation time (eTable 3). These variables, including driving pressure and mechanical power, will be compared among the groups using Student's *t* test. Also, the trend of the ventilator variables every 30 minutes for the first three hours will be compared between the groups using mixed-effect linear models, considering an interaction term between time and group and the patients as random effects.

Outcomes:

Percentage of time in the optimal, acceptable and unacceptable zone for at least 30 seconds during the first three hours of ventilation or until extubation, if extubated earlier, and according to the postoperative total recorded ventilation time (eTable 4).

The number of episodes where the ventilation stays in one of the three zone for at least 30 consecutive seconds will be calculated. Then, this number will be corrected by the total duration of ventilation as:

$$\%_{UZ} = (T_{UZ} / DV) \times 100$$

Where $\%_{UZ}$ is the percentage of time in a zone, T_{UZ} is the time in seconds where the ventilation stays in the specific zone for at least 30 consecutive seconds, and DV is the total duration of ventilation in seconds. This number will be reported as mean ± standard deviation and median (interquartile range). The effect of the intervention will be estimated with a Student's *t*–test and reported as the mean difference between the two groups. The consistency of the findings of the Student's *t*-test will be tested using a bootstrapped Student's *t*-test with 1,000

replications. If a very nonsymmetrical distribution is found, we will use the best distribution that fits the data.

Percentage of breaths in the optimal, acceptable and unacceptable zone according to the total number of breaths during the first three hours of ventilation or until extubation, if extubated earlier, and according to the postoperative total recorded ventilation time. (eTable 4).

The percentage of breaths in the three zones will be reported as number and percentages (according to the total number of breaths and not according to the number of patients) and the effects of the intervention will be estimated with risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ^2 tests for hypothesis testing.

Number of successful extubations within the first 6, 12 and 24hours after surgery (eTable 5).

The effects of the intervention on the number of successful extubation within the first 6, 12 and 24 hours of mechanical ventilation after admission on the ICU will be reported as number and percentages and estimated with risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ^2 tests for hypothesis testing. These findings will be confirmed using logistic models adjusted by the duration of surgery, total intravenous sedatives dosage and the time from ICU admission until a rectal temperature >35.5°C.

Total Time until extubation (considering the time from ICU admission until extubation) (eTable 5).

The time until extubation will be assessed using Kaplan–Meier curves, and hazard ratios with a 95% confidence interval will be calculated with Cox proportional hazard models without adjustment for covariates. The proportional hazard assumptions will be tested and alternative parametric survival models will be used if the proportionality assumption is not sustained. These findings will be confirmed using Cox proportional hazard models adjusted by the duration of surgery, total intravenous sedatives dosage and the time from ICU admission until a rectal temperature >35.5°C.

Time until first spontaneous breathing (considering the time from ICU admission until first spontaneous breathing) (eTable 5).

The time until first spontaneous breathing will be assessed using Kaplan–Meier curves, and hazard ratios with a 95% confidence interval will be calculated with Cox proportional hazard models without adjustment for covariates. The proportional hazard assumptions will be tested and alternative parametric survival models will be used if the proportionality assumption is not sustained. These findings will be confirmed using Cox proportional hazard models adjusted by the duration of surgery the duration of surgery, total intravenous sedatives dosage and the time from ICU admission until a rectal temperature >35.5°C.

The total number of alarms and intervention within the first 3 hours or until extubation (eTable 5).

The total number of alarms and intervention within the first 3 hours or until extubation will be reported as mean ± standard deviation and median (interquartile range). The effect of the intervention will be estimated with a

Student's *t*–test and reported as the mean difference between the two groups. The consistency of the findings of the Student's *t*-test will be tested using a bootstrapped Student's *t*-test with 1,000 replications. If a very nonsymmetrical distribution is found, we will use the best distribution that fits the data.

ICUmortality (eTable 5).

The effects of the intervention on ICU mortality rate will be reported as number and percentages and estimated with risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ^2 tests for hypothesis testing.

ICU readmission (eTable 5).

The effects of the intervention on ICU readmission rate will be reported as number and percentages and estimated with risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ^2 tests for hypothesis testing.

30-Day mortality (eTable 5).

Survival within 30 days will be assessed using Kaplan–Meier curves, and hazard ratios with a 95% confidence interval will be calculated with Cox proportional hazard models without adjustment for covariates. The proportional hazard assumptions will be tested and alternative parametric survival models will be used if the proportionality assumption is not sustained.

ICU length of stay (eTable 5).

The effects of the intervention on ICU length of stay will be estimated with generalized linear models considering distributions that will fit a possible heavy right–tailed distribution without zero (such as truncated Poisson, gamma distribution or inverse Gaussian), choosing the best fit according to model's deviance.

Postoperative pulmonary complications (eTable 5).

The effects of the intervention on the incidence of postoperative pulmonary complications will be reported as number and percentages and estimated with risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ^2 tests for hypothesis testing.

Percentage of breaths that the $EtCO_2$ and/or SpO_2 measurements were missing or of a quality of < 51% (eTable 5).

The percentage of breaths that the $EtCO_2$ or SpO_2 measurements were missing or of a quality of < 51% will be reported as number and percentages (according to the total number of breaths and not according to the number of patients) and the effects of the intervention will be estimated with risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ^2 tests for hypothesis testing.

The median acceptance score (1-10) of the nurse (eTable 5).

The median acceptance score of the nurse will be reported as mean ± standard deviation and median (interquartile range). The effect of the intervention will be estimated with a Student's *t*–test and reported as the mean difference between

the two groups. The consistency of the findings of the Student's *t*-test will be tested using a bootstrapped Student's *t*-test with 1,000 replications. If a very nonsymmetrical distribution is found, we will use the best distribution that fits the data.

Per–protocol analysis: In creating a per–protocol population we will exclude patients who had one or more major protocol violations. Patients receiving the mode of the group that they were not assigned to will be excluded for the per–protocol analysis of the primary outcome. The patient will be included for the per protocol analysis of the primary outcome during the first three hours, if the change in mode occurred after the first three hours of ventilation.

Patients that died or had a re-sternotomy (for example due to bleeding) during the first three hours (for the first three hours per protocol analysis) or during the logging of the datalogger (for the overall recorded per protocol analysis) will be excluded for the per–protocol analysis of the primary outcome.

As treated analysis: In creating a as treated analysis we will analyze the recorded ventilation data according to the treatment they actually received. Patients receiving the mode of the group that they were not assigned to will be excluded for the per–protocol analysis of the primary outcome.

Subgroup analyses: Treatment effects on the primary outcome will be analyzed according to the following subgroups: 1) patient who were successfully extubated before or after the median postoperative mechanical ventilation time (eTable 6); 2) subgroup analysis based on the intraoperative mechanical ventilation time: shorter or longer than the median intraoperative mechanical ventilation time (eTable 7); 3) patients with PaO_2 / FiO_2 below or above the median PaO_2 / FiO_2

at admission on the ICU (eTable 8); The effects on subgroups will be evaluated according to the interaction effects between each subgroup and the study arms by generalized linear models considering zero–inflated distributions and presented in a forest plot.

CONCLUSION

According to best research practice, we reported here the pre–specified detailed statistical analysis plan prior to locking the database and starting analyses. This document guarantees against reporting bias, selective reporting and data–driven results, as such enhancing the utility of the reported results.

TABLES

eTable 1

Predefined zones of ventilation

	Optimal	Acceptable*	Not acceptable*
Tidal volume (ml/kg PBW)	**6-8 (proposed 4-8)**	**>8-12**	**>12**
$EtCO_2$ (mmHg)	**30-45**	**<30-25 >45-50**	**<25 ≥51**
Peak pressure (cmH_2O)	**≤30**	**31-35**	**>35**
SpO_2 (%)	**93-98 (≥93 if FIO_2 <40%)**	**93-85 ≥98**	**<85**

***for analysis calculated as lasting >30 seconds and per breathing.**

eTable 2 – Baseline characteristics of the patients

	INTELLiVENT-ASV	Conventional ventilation
Age, years	Mean ± SD	Mean ± SD
Male sex	N / Total (%)	N / Total (%)
BMI, kg/m^2	Mean ± SD	Mean ± SD
PBW, kg	Mean ± SD	Mean ± SD
SAPS II score	Mean ± SD	Mean ± SD
APACHE IV score	Mean ± SD	Mean ± SD
Euroscore II	Mean ± SD	Mean ± SD
Tobacco use	N / Total (%)	N / Total (%)
History of alcohol abuse	N / Total (%)	N / Total (%)
Edmonton frailty scale	N / Total (%)	N / Total (%)
Medical history		
COPD GOLD ≥ 2	N / Total (%)	N / Total (%)
Asthma	N / Total (%)	N / Total (%)
OSAS	N / Total (%)	N / Total (%)
CVA	N / Total (%)	N / Total (%)
Diabetes Mellitus	N / Total (%)	N / Total (%)
Hypertension	N / Total (%)	N / Total (%)
NYHA ≥ 2	N / Total (%)	N / Total (%)
CKD (MDRD <30ml/min)	N / Total (%)	N / Total (%)
Preoperative left ventricle function (%)		
Normal (EF = ≥55%)	N / Total (%)	N / Total (%)
Moderate impaired (EF = 30-54%)	N / Total (%)	N / Total (%)
Severely impaired (EF = <30%)	N / Total (%)	N / Total (%)
Type of surgery		
CABG	N / Total (%)	N / Total (%)
Off-pump coronary artery bypass	N / Total (%)	N / Total (%)
Valve surgery	N / Total (%)	N / Total (%)
CABG + valve surgery	N / Total (%)	N / Total (%)
Aortic ascendens surgery	N / Total (%)	N / Total (%)
Aortic ascendens + CABG/valve	N / Total (%)	N / Total (%)
Extracorporeal circulation (minutes)	Median (IQR)	Median (IQR)
Aortic occlusion time (minutes)	Median (IQR)	Median (IQR)
First postoperative CKMB (U/L)	Median (IQR)	Median (IQR)

APACHE: Acute Physiology And Chronic Health Evaluation; ASV: Adaptive Support Ventilation; BMI: body mass index; CABG: coronary artery bypass grafting; CKD: chronic kideny disease; CKMB: creatine kinase myocardial band; COPD: Chronic Obstructive Pulmonary Disease; CVA: cerebral vascular accident; EF: ejection fraction; SAPS: Simplified Acute Physiology Score; PBW: predicted body weight; IQR: interquartile range; SD: standard deviation.

eTable 3 – Ventilatory variables over time

	At ICU admission			After 30 minutes			After 60 minutes			After 90 minutes		
	I-ASV	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**
Number of patients	N	N		N	N		N	N		N	N	
Tidal volume, mL/kg PBW	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
PEEP, cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Plateau pressure, cmH_2O*	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Driving pressure, cmH_2O*	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Mechanical Power (J/min)*	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Respiratory rate, bpm	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Static compliance, mL/cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
FiO_2	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
SpO_2, %	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
$EtCO_2$, mmHg	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
PaO2 / FiO2	Mean ± SD	Mean ± SD		[redacted]			Mean ± SD	Mean ± SD		[redacted]		
$EtCO_2$ / $PaCO_2$	Mean ± SD	Mean ± SD					Mean ± SD	Mean ± SD				
Arterial pH	Mean ± SD	Mean ± SD					Mean ± SD	Mean ± SD				

	At ICU admission			After 120 minutes			After 150 minutes			After 180 minutes		
	I-ASV	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**
Number of patients	N	N		N	N		N	N		N	N	
Tidal volume, mL/kg PBW	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
PEEP, cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Plateau pressure, cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Driving pressure, cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Mechanical Power (J/min)	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Respiratory rate, bpm	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Static compliance, mL/cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
FiO_2	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
SpO_2, %	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
$EtCO_2$ mmHg	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	

	At ICU admission			After 6 hours			After 12 hours			After 24 hours		
	I-ASV	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**
Number of patients	N	N		N	N		N	N		N	N	
Tidal volume, mL/kg PBW	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
PEEP, cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Peak pressure, cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Respiratory rate, bpm	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	

Static compliance, mL/cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
FiO_2	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
SpO_2, %	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
$EtCO_2$, mmHg	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
	At ICU admission			**After 36 minutes**			**After 48 minutes**			**After 72 hours**		
	I-ASV	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**	**I-ASV**	**Conventional**	***p* value**
Number of patients	N	N		N	N		N	N		N	N	
Tidal volume, mL/kg PBW	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
PEEP, cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Peak pressure, cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Respiratory rate, bpm	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Static compliance, mL/cmH_2O	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
FiO_2	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
SpO_2, %	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
$EtCO_2$ mmHg	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	

PBW: predicted body weight; bpm: breaths per minute; PEEP: positive end-expiratory pressure; SD: standard deviation

* based on manually retrieved values during both an inspiratory and expiratory hold of at least 5 seconds

eTable 4 – Intention-to-treat, as treated and per protocol analysis of the percentage of breaths and time in the optimal, acceptable and unacceptable zones during the first 3 hours of postoperative mechanical ventilation or extubation, and for all recorded breaths.

	Intention-to-treat analysis				As treated analysis				Per protocol analysis			
First 3 hours of mechanical ventilation	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**
Percentage of breaths in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Percentage of time* in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
All recorded breaths and time												
Percentage of breaths in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Percentage of time* in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	

eTable 5 – Secondary outcomes	Intention-to-tread				Per-protocol			
	INTELLiVENT-ASV	**Conventional mode**	**Effect Estimate (95% CI)**	**P value**	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	**P value**
Ventilation time								
Intubation – successful extubation* Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference		Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	
ICU admission – successful extubation* Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference		Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	
Weaning time								
Stop sedation – successful extubation* Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference		Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	
Time until spontaneous breathing**								
Intubation – spontaneous breathing Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference		Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	
ICU admission – spontaneous breathing Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference		Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	
Stop sedation – spontaneous breathing Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference		Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	
Mortality								
ICU	N / Total (%)	N / Total (%)	Risk ratio		N / Total (%)	N / Total (%)	Risk ratio	
30-day	N / Total (%)	N / Total (%)	Hazard ratio		N / Total (%)	N / Total (%)	Hazard ratio	
Length of stay								
ICU Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference		Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	
ICU readmissions								
Readmission <72 hours after discharge	N / Total (%)	N / Total (%)	Risk ratio		N / Total (%)	N / Total (%)	Risk ratio	
Number of alarms								
First 3 hours (n/3 hours) Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference		Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	

All recorded time (n/hour) Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference
Times SpO2 measurement of <85% during mechanical ventilation*						
First 3 hours (n/3 hours) Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference
All recorded time (n/hour) Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference
Lowest measured SpO_2 over all recorded time.	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference
Missing measurement**: all recorded time $EtCO_2$ SpO_2	 Mean ± SD Median (IQR) Mean ± SD Median (IQR)	 Mean ± SD Median (IQR) Mean ± SD Median (IQR)	 Mean difference Mean difference	 Mean ± SD Median (IQR) Mean ± SD Median (IQR)	 Mean ± SD Median (IQR) Mean ± SD Median (IQR)	 Mean difference Mean difference
Number of interventions						
First 3 hours (n/3 hours) Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference
All recorded time (n/hour) Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference
Pulmonary complication (first 72 hours)						
Pneumonia	N / Total (%)	N / Total (%)	Risk ratio	N / Total (%)	N / Total (%)	Risk ratio
Pneumothorax	N / Total (%)	N / Total (%)	Risk ratio	N / Total (%)	N / Total (%)	Risk ratio
Atelectasis	N / Total (%)	N / Total (%)	Risk ratio	N / Total (%)	N / Total (%)	Risk ratio
Overall	N / Total (%)	N / Total (%)	Risk ratio	N / Total (%)	N / Total (%)	Risk ratio
Acceptance score						
Score (1-10) Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean difference

*Measurement with a quality index >50%

** Measurement with a quality index <51%

eTable 6 – Intention-to treat analysis and per protocol analysis of the percentage of breaths and time in the optimal, acceptable and unacceptable zones during the first 3 hours of postoperative mechanical ventilation or extubation, and for all recorded breaths for patient who were successfully extubated before or after the median postoperative mechanical ventilation time.

	Intention-to-treat analysis				As treated analysis				Per protocol analysis			
First 3 hours of mechanical ventilation	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**
Percentage of breaths in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Percentage of time* in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
All recorded breaths and time												
Percentage of breaths in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Percentage of time* in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	

*for at least 30 seconds in a zone

eTable 7 – Intention-to treat analysis and per protocol analysis of the percentage of breaths and time in the optimal, acceptable and unacceptable zones during the first 3 hours of postoperative mechanical ventilation or extubation, and for all recorded breaths for patients with a intraoperative mechanical ventilation time that was shorter or longer than the median intraoperative mechanical ventilation time.

	Intention-to-treat analysis				As treated analysis				Per protocol analysis			
First 3 hours of mechanical ventilation	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**
Percentage of breaths in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Percentage of time* in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
All recorded breaths and time												
Percentage of breaths in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Percentage of time* in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	

*for at least 30 seconds in a zone

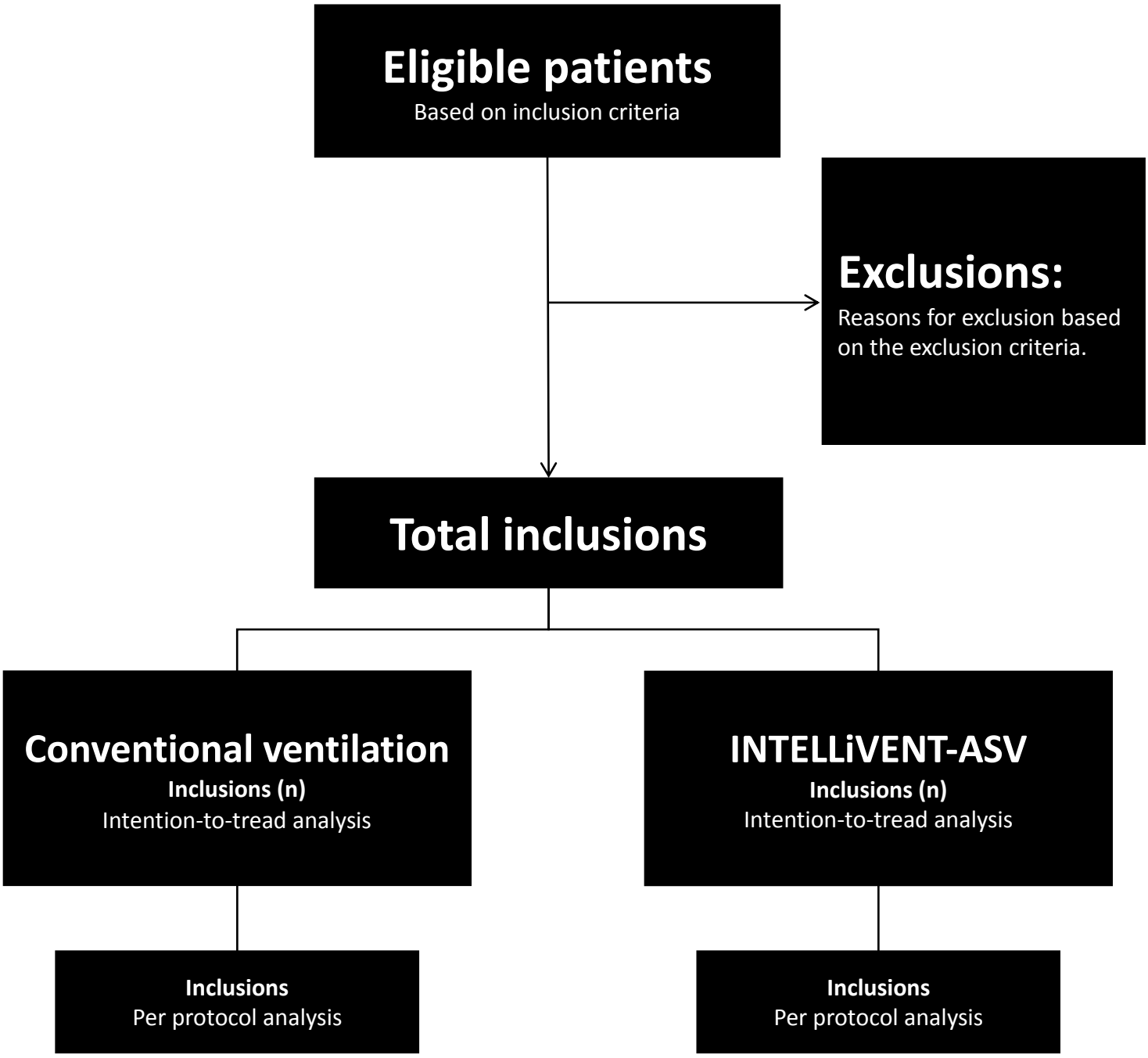
eTable 8 – Intention-to treat-analysis, as treated analysis and per protocol analysis of the percentage of breaths and time in the optimal, acceptable and unacceptable zones during the first 3 hours of postoperative mechanical ventilation or extubation, and for all recorded breaths for patients with PaO_2 / FiO_2 below or above the median PaO_2 / FiO_2 at admission on the ICU.

	Intention-to-treat analysis				As treated analysis				Per protocol analysis			
First 3 hours of mechanical ventilation	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**	**INTELLiVENT-ASV**	**Conventional mode**	**Effect Estimate (95% CI)**	***p* value**
Percentage of breaths in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Percentage of time* in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
All recorded breaths and time												
Percentage of breaths in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Percentage of time* in:												
Optimal zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference		Median (IQR)	Median (IQR)	difference	
Acceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	
Unacceptable zone	Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean		Mean ± SD	Mean ± SD	Mean	
Median (IQR)	Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference		Median (IQR	Median (IQR	difference	

*for at least 30 seconds in a zone

FIGURE LEGENDS

Figure 1 – Flow of the patients in the POSiTIVE trial



LIST OF ABBREVIATIONS

ARDS: acute respiratory distress syndrome

APACHE: Acute Physiology And Chronic Health Evaluation

CONSORT: Consolidated Standards of Reporting Trials

COPD: chronic obstructive pulmonary disease

DSMB: Data and Safety Monitoring Board

GOLD: Global Initiative for Chronic Obstructive Lung Disease

ICH-GCP: International Conference on Harmonization - Good Clinical Practice

ICU: intensive care unit

IQR: interquartile range

LOS: length of stay

PBW: predicted body weight

SAP: statistical analysis plan

SAPS: Simplified Acute Physiology Score

SBT: Spontaneous breathing trial

SD: standard deviation

DECLARATIONS

Ethics approval and consent to participate: The Medical Research Ethics Committees United (MEC-U), Nieuwegein, The Netherlands, under reference number R16.054.

Consent for publication: Not applicable.

Availability of data and material: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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AJR, ASN, DMP, RA, AN, HHM, MJS, AGJH, designed the study, the statistical analysis plan and approved the initially submitted version of this manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. www.ClinicalTrials.gov; Identifier: NCT03180203

2. Dwand K, Gamble C, Williamson PR, Altaman DG. Reporting of clinical trials: a review of research funders' guidelines. Trials 2008;9:66

3. The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526–33.

4. Lellouche F, Bouchard P-A, Simard S, L'Her E, Wysocki M. Evaluation of fully automated ventilation: a randomized controlled study in post-cardiac surgery patients. Intensive Care Med (2013) 39:463–471.

5. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342:1301–8.

6. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, et al. Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 2016;42:1567-75.

7. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81(3):515-26.

8. McCullagh P, Nelder JA. Generalized linear models. 2nd ed. (Monographs on Statistics and Probability 37). London: Chapman & Hall; 1989.