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Fully automated postoperative ventilation in cardiac surgery patients: a randomised clinical trial

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Abstract

Background: Ensuring that lung-protective ventilation is achieved at scale is challenging in perioperative practice. Fully automated ventilation may be more effective in delivering lung-protective ventilation. Here, we compared automated lung-protective ventilation with conventional ventilation after elective cardiac surgery in haemodynamically stable patients.

Methods: In this single-centre investigator-led study, patients were randomly assigned at the end of cardiac surgery to receive either automated (adaptive support ventilation) or conventional ventilation. The primary endpoint was the proportion of postoperative ventilation time characterised by exposure to predefined optimal, acceptable, and critical (injurious) ventilatory parameters in the first three postoperative hours. Secondary outcomes included severe hypoxaemia (Spo_2 <85%) and resumption of spontaneous breathing. Data are presented as mean (95% confidence intervals [CIs]).

Results: We randomised 220 patients (30.4% females; age: 62–76 yr). Subjects randomised to automated ventilation (n=109) spent a 29.7% (95% CI: 22.1–37.4) higher mean proportion of postoperative ventilation time receiving optimal postoperative ventilation after surgery (P<0.001) compared with subjects receiving conventional postoperative ventilation (n=111). Automated ventilation also reduced the proportion of postoperative ventilation time that subjects were exposed to injurious ventilatory settings by 2.5% (95% CI: 1–4; P=0.003). Severe hypoxaemia was less likely in subjects randomised to automated ventilation (risk ratio: 0.26 [0.22–0.31]; P<0.01). Subjects resumed spontaneous breathing more rapidly when randomised to automated ventilation (hazard ratio: 1.38 [1.05–1.83]; P=0.03).

Conclusions: Fully automated ventilation in haemodynamically stable patients after cardiac surgery optimised lung-protective ventilation during postoperative ventilation, with fewer episodes of severe hypoxaemia and an accelerated resumption of spontaneous breathing.

Clinical trial registration: NCT03180203.

Keywords: automated ventilation; cardiac surgery; intensive care unit; lung protection; mechanical ventilation; postoperative ventilation; protective ventilation

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Editor's key points

- Injurious perioperative ventilation settings are associated with poorer outcomes.
- Automated ventilatory control, which aims to minimise exposure to injurious ventilatory parameters, may help prevent injurious ventilation.
- In this single-centre randomised control led trial, patients were randomised to receive either conventional or fully automated weaning from ventilatory support after cardiac surgery.
- Automated ventilation reduced the period of time that subjects were exposed to potentially injurious ventilatory settings, and episodes of hypoxaemia.
- These data, obtained in haemodynamically stable cardiac surgical patients at lower risk of postoperative complications, suggest that automated ventilation warrants exploration in higher-risk noncardiac and cardiac surgical patients.

High tidal volume during postoperative ventilation is a risk factor for organ dysfunction, pulmonary complications, and prolonged ICU stay in cardiac surgery patients.[1] High PEEP may prevent postoperative complications and shortens ICU stay in cardiac surgery patients who present with hypoxaemia upon arrival in the ICU.[2] Physiological and clinical studies suggest that arterial hyperoxia and also hypoxia are better avoided in ventilated patients, as both have an association with mortality.[3–9]

Automated modes of ventilation are increasingly becoming available for clinical use.[10,11] The common goals of automated ventilatory modes are to tailor ventilator settings to patient's needs, facilitate earlier recognition of the ability to breathe spontaneously with subsequent smooth weaning from the ventilator,[12–14] and deliver lung-protective ventilator settings.[11,15] INTELLiVENT-Adaptive Support Ventilation (ASV) is a fully automated, or closed-loop, ventilation mode that consists of pressure-controlled ventilation or pressure support ventilation depending on a patient's respiratory activity. In fully automated ventilation mode, tidal volume, pressure levels (including PEEP), minute ventilation, and the oxygen fraction in inspired air are controlled solely by the ventilator.[16,17]

Previous studies have shown INTELLiVENT-ASV to be capable of applying ventilation with safe ventilator settings in critically ill patients.[18–27] The aim of the current study was to compare INTELLiVENT-ASV with conventional ventilation during postoperative ventilation after uncomplicated cardiac surgery. We hypothesised that fully automated mode of ventilation would be more likely to deliver lung-protective ventilation during weaning after cardiac surgery.

Methods

Study design and oversight

The Postoperative INTELLiVENT-ASV Ventilation study was an investigator-initiated, single-centre, parallel-group, randomised clinical trial, conducted at the ICU of a tertiary teaching hospital in Eindhoven, Netherlands. The manufacturer of the ventilator was not involved. The study protocol was approved by the local Institutional Review Board (R16.054) and registered at ClinicalTrials.gov (study identifier: NCT03180203). A statistical analysis plan was constructed before cleaning and closing the database; the final plan and a table describing changes to the original analysis plan are available in the Supplementary material. Written informed consent was obtained from all individual participants before surgery.

Inclusion criteria

Subjects were eligible if they were scheduled for elective cardiac surgery requiring postoperative invasive ventilation in the ICU.

Exclusion criteria

Before surgery, patients were excluded if aged <18 yr, BMI >35 kg m^{-2}, have a history of pneumonectomy or lobectomy, presence of chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease Class III or IV), or if they were already enrolled in another interventional trial. After cardiac surgery, patients were ineligible if extracorporeal support was required after surgery, or if they were deemed by the attending clinician to be haemodynamically unstable. Fast-track cardiac surgery patients were also ineligible as they were planned to receive postoperative ventilation in the PACU where the automated mode was not available.

Randomisation and masking

Subjects were randomised in a 1:1 ratio to fully automated ventilation (the 'automated group') or conventional ventilation ('conventional group') before the start of surgery. Local investigators performed randomisation with a web-based randomisation programme that used random block sizes. Physicians and nurses caring for the subjects in the ICU could not be blinded because of the nature of the intervention. The investigators who performed the analyses (AJRDB and ASN) and the radiologist (JRL), though, remained blind for randomisation at all times.

Perioperative care

Standardised perioperative care was followed according to local guidelines. Typically, one board-certified ICU nurse cared for a maximum of two patients. Nurses were responsible for adjusting ventilator settings; doctors could be consulted at all times. Arterial blood gases were performed regularly. Extubation criteria were similar for both groups and followed the local guideline. For additional details on standard care, see Supplementary data.

Study interventions

The same type of ventilator (Hamilton-S1; Hamilton Medical, Rhäzüns, Switzerland) was used for all subjects. All attending ICU nurses and physicians were trained and qualified to use this ventilator and the INTELLiVENT-ASV and the volume-controlled ventilation mode.

In the automated group, ventilation started with volume-controlled ventilation. INTELLiVENT-ASV was initiated as soon as the first blood gas analysis was available, typically within 15 min after arrival in the ICU. After initiating INTELLiVENT-ASV, minute ventilation V_T, pressure levels (including PEEP), and F_{IO_2} were automatically adjusted by the ventilator to provide invasive ventilation within appropriate

Table 1 Zones of ventilation used to define the primary outcome (adapted from Lellouche and colleagues[23]). Et_{CO_2}, end-tidal carbon dioxide; F_{IO_2}, inspired fraction of oxygen; PBW, predicted body weight; Sp_{O_2}, oxygen pulse oximetry.

	Optimal zone	Acceptable zone	Critical zone
Tidal volume (ml kg^{-1}) PBW	≤8	8–12	>12
	and	or	or
Maximum airway pressure (cm H_2O)	<31	31–36	≥36
	and	or	or
Et_{CO_2} (kPa)	4.0–6.1	3.3–4.0 or 6.1–6.8	<3.3 or ≥6.8
	and	or	or
Sp_{O_2} (%)	93–98 or ≥93 if F_{IO_2} ≤40%	≥98 or 85–93	<85
Definition	If any present: *critical zone*	If not in the *optimal zone* and none of the *critical zone* is present: *acceptable zone*	All must be present: *optimal zone*
Missing	If all parameters are missing, *zone* is missing. If parameters are missing, but one is available and it is in the *critical zone*, *zone* is defined as *critical*. If parameters are missing, but one is available and it is not in the *critical zone*, *zone* is defined as *missing*.		

ranges of Et_{CO_2} and Sp_{O_2}. Thus, neither V_T and minute volume nor PEEP and F_{IO_2} were to be adjusted by the attending ICU nurse or doctor. For additional details on settings with INTELLiVENT-ASV, see the Supplementary material and Supplementary Fig. S1.

In the conventional group, ventilation also started with volume-controlled ventilation, and pressure support was initiated as soon as the patient was able to trigger the ventilator, which was typically tested every 15 min after cessation of postoperative sedation. V_T, maximum airway pressure (P_{max}), and ventilatory frequency (VF) were manually titrated to have V_T ≤7 ml kg^{-1} predicted body weight (PBW); P_{max} <30 cm H_2O. Ventilatory frequency was titrated to have Et_{CO_2} between 4.7 and 6.4 kPa. PEEP and F_{IO_2} were titrated using a low PEEP–F_{IO_2} table to have Sp_{O_2} stay between 93% and 98%.[16] For additional details on settings with conventional, see the Supplementary material and Supplementary Fig. S1.

Data collection

'Breath-by-breath' ventilation data were collected using a StudyRecorder (version 1.5; Hamilton Medical) connected to study ventilators. Every 30 min, an inspiratory hold was performed to measure plateau pressure and an expiratory hold to measure total PEEP. Driving pressure and mechanical power of ventilation were calculated using the following formulae:

Driving pressure=plateau pressure−PEEP

Mechanical power (J min^{-1})=0.098*V_T (L)*VF* (maximum airway pressure−driving pressure*0.5)

Inspiratory and expiratory holds were not performed during spontaneous breathing, meaning that driving pressure could only be estimated and mechanical power only be calculated when a patient was receiving pressure controlled with INTELLiVENT-ASV in the automated group or volume-controlled ventilation in the control group (additional details are provided in Supplementary material).

Primary outcome

The primary outcome was the proportion of time spent in three predefined and previously used zones of ventilation in the first 3 h of postoperative ventilation (Table 1).[23]

Secondary outcomes

We assessed the following secondary endpoints:

(i) The proportion of breaths within each predefined ventilatory zone in the first 3 h of postoperative ventilation; outcomes regarding proportion of time spent in the three zones of ventilation were also reanalysed using the complete ventilation time instead of the first three postoperative hours
(ii) Incidence of severe hypoxaemia (percentage of breaths with Sp_{O_2} <85% if Sp_{O_2} quality index was ≥50%)
(iii) Time to spontaneous breathing (time from ICU admission until more than or equal to five consecutive spontaneous breaths)
(iv) Duration of postoperative ventilation
(v) Duration of weaning (time from cessation of sedatives until tracheal extubation)
(vi) Proportion of failed extubations (re-intubation within 48 h after extubation, excluding patients re-intubated for re-sternotomy) and development of postoperative pulmonary complications (composite of pneumonia, pneumothorax, or severe atelectasis)
(vii) ICU length of stay and readmission
(viii) ICU and 30-day mortality

Statistical analysis

All analyses were performed in a modified intention-to-treat population. Reasons for exclusion until ICU admission (i.e.

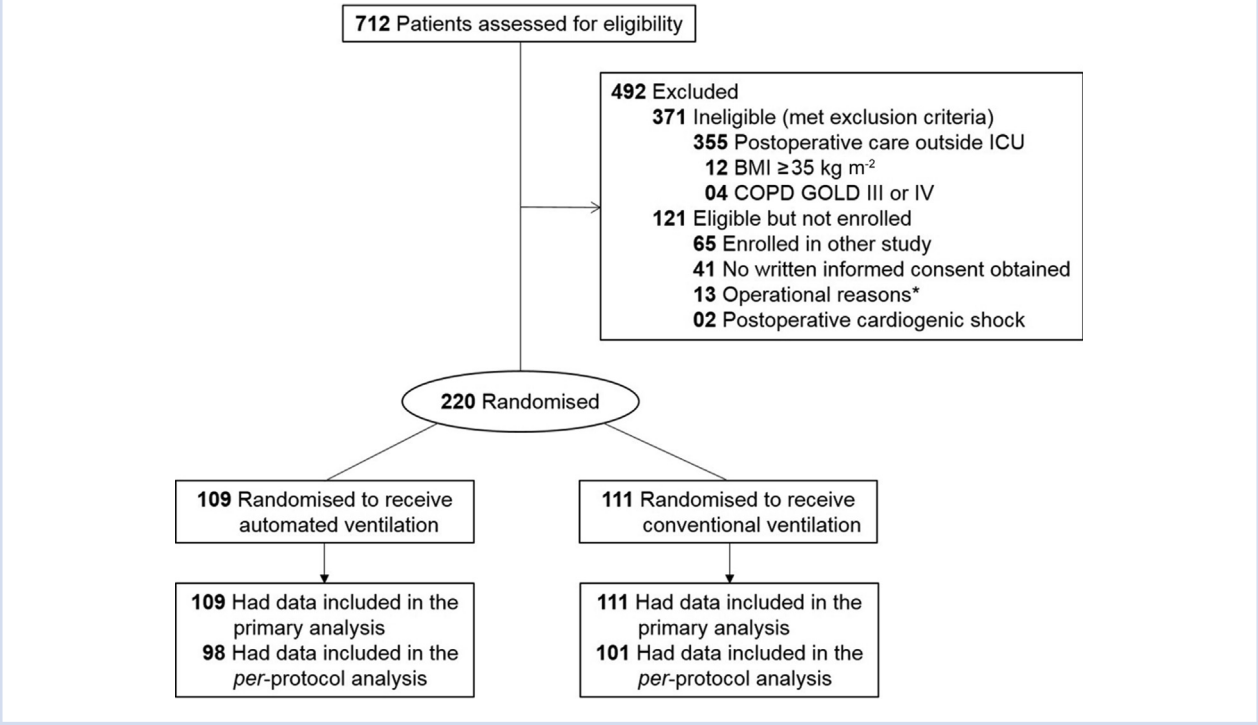

Fig 1. Flow of patients in the trial. COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease. *No study ventilator available.

after randomisation) were haemodynamic instability at the end of surgery, with or without need to continue extracorporeal support after surgery, and incidentally the unavailability of a ventilator that could provide the fully automated ventilation mode. In the per-protocol analysis, patients who had one or more major protocol violations were excluded. Details are provided in the Supplementary material.

Descriptive data are reported as numbers and percentages, means (standard deviation), or medians (inter-quartile ranges). Comparison of ventilatory parameters between groups over time was done using mixed-effect longitudinal models with random intercepts for patients. For analysis of the primary outcome, Student's *t*-test was used with 95% confidence interval (CI), and results are presented as mean differences (MDs). For outcomes assessing proportions of breaths, the denominator was the total number of breaths. Secondary binary outcomes were assessed with risk ratio and 95% CI calculated with Wald likelihood ratio approximation test and χ^2 tests for hypothesis testing.

The effects of the intervention on time to spontaneous breathing, duration of weaning and ventilation, and 30-day mortality were assessed using Kaplan–Meier survival curves and reported as hazard ratios with 95% CI calculated from a Cox proportional hazard model. The Schoenfeld residuals against the transformed time were used to test the proportional hazard assumptions. Survival time was calculated from time of randomisation until time of the outcome. The effect of the intervention on ICU length of stay was estimated with generalised linear models using inverse Gaussian distribution.

In pre-specified exploratory analyses, the effects of automated ventilation on the proportions of time spent in critical zone were investigated in subgroups based on the following patient categories: (i) according to intraoperative ventilation time (shorter or longer than the median) and (ii) according to $Pa_{O_2}/F_{I_{O_2}}$ (below or above the median at ICU admission). The effects in the subgroups were evaluated by generalised linear models considering Gaussian distribution. Although reported in the statistical analysis plan, an exploratory analysis according to duration of postoperative ventilation was not performed as this characteristic might be influenced by the intervention.

In one *post hoc* analysis, the ventilation zones were based on the four individual elements (i.e. maximum airway pressure, tidal volume, Et_{CO_2}, and Sp_{O_2}). In a second *post hoc* analysis, groups were compared with respect to proportion of breaths: (i) with hyperoxia (Sp_{O_2} >97%), hypoxaemia (Sp_{O_2} <90%), and normoxia (Sp_{O_2} between 90% and 97%); (ii) with a P_{max} of ≤30 cm H_2O; and (iii) with a driving pressure ≤15 cm H_2O. Details are provided in the Supplementary material.

All analyses were performed using R software, version 3.4.1 (R Core Team, Vienna, Austria). Significance level for all outcomes was 0.05, without adjustment for multiple comparisons. All secondary outcomes and analyses were exploratory. Reported *P*-values are two sided, and because the amount of missing data is negligible, only complete case analysis was carried out.

Sample size calculation

The study sample size was calculated using G*power (version 3.1.9.2; G*power Team, Kiel, Germany). We estimated that a sample size of 196 subjects would provide 95% power to detect

Table 2 Subject characteristics. Data are median (25–75% quartile) or no. (%). APACHE, Acute Physiology and Chronic Health Evaluation; CABG, coronary artery bypass graft; CK-MB, creatine kinase-myocardial band isoenzyme; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OSA, obstructive sleep apnoea; PBW, predicted body weight; SAPS, Simplified Acute Physiology Score; TIA, transient ischaemic attack.

	Fully automated ventilation (*n*=109)	Conventional ventilation (*n*=111)
Age (yr)	70 (62–76)	70 (63–76)
Male sex	73 (67.0)	80 (72.1)
PBW (kg)	66.0 (59.7–75.1)	68.3 (61.0–73.3)
BMI (kg m^{-2})	26.0 (24.2–29.2)	26.5 (24.5–29.0)
SAPS II	31 (29–39)	33 (28–39)
APACHE IV	41 (33–49)	38 (32–48)
Euroscore II	1.6 (1.0–3.6)	1.6 (1.0–2.8)
Edmonton Frail Scale	3 (2–4)	3 (2–5)
Smoking		
No	39 (35.8)	47 (42.3)
Current	19 (17.4)	20 (18.0)
Former	51 (46.8)	44 (39.6)
Use of alcohol	65 (59.7)	71 (64.0)
COPD	7 (6.4)	12 (10.8)
Asthma	8 (7.3)	6 (5.4)
OSA	7 (6.4)	10 (9.0)
Diabetes mellitus	28 (25.7)	15 (13.5)
Hypertension	68 (62.4)	65 (58.6)
CVD or TIA	14 (12.9)	17 (15.3)
Heart failure	95 (87.9)	94 (85.4)
NYHA classification		
I	19 (17.6)	16 (14.5)
II	51 (47.2)	60 (54.5)
III	24 (22.2)	17 (15.5)
IV	1 (0.9)	1 (0.9)
Peripheral artery disease	19 (17.4)	14 (12.6)
Chronic kidney disease (%)	23 (21.1)	28 (25.2)
LVEF	50 (35–56)	54 (45–60)
Right ventricular function		
Good	103 (97.2)	95 (94.1)
Moderate	2 (1.9)	5 (5.0)
Poor	1 (0.9)	1 (1.0)
Aortic valve disease		
None	54 (49.5)	47 (42.3)
Moderate insufficiency	5 (4.6)	5 (4.5)
Severe insufficiency	10 (9.2)	7 (6.3)
Moderate stenosis	6 (5.5)	4 (3.6)
Severe stenosis	34 (31.2)	48 (43.2)
Mitral valve disease		
None	71 (65.1)	69 (62.2)
Moderate insufficiency	8 (7.3)	10 (9.0)
Severe insufficiency	29 (26.6)	29 (26.1)
Severe stenosis	1 (0.9)	3 (2.7)
Tricuspid valve disease		
None	96 (88.1)	90 (81.1)
Moderate insufficiency	8 (7.3)	14 (12.6)
Severe insufficiency	5 (4.6)	7 (6.3)
Preoperative use of levosimendan	4 (3.7)	5 (4.5)
Type of surgery		
CABG	8 (7.3)	16 (14.4)
Valve surgery	48 (44.0)	47 (42.3)
CABG+valve surgery	30 (27.5)	36 (32.4)
Off-pump CABG	14 (12.8)	2 (1.8)
Aortic repair	8 (7.3)	10 (9.0)
Myxoma excision	1 (0.9)	0 (0.0)
Duration of extracorporeal circulation (min)	114 (87–157)	106 (77–145)
Duration of aortic occlusion (min)	77 (57–109)	71 (53–97)
Perioperative use of sedatives and analgesia		
Etomidate (mg)	50 (50–70)	50 (50–50)
Rocuronium (mg)	200 (200–200)	200 (200–200)
Propofol (mg)	1437 (1135–1760)	1404 (1130–1782)
Midazolam (mg)	2.5 (0–5)	5 (0–5)
Opiates		
Morphine (mg)	25 (25–25)	25 (25–25)
Alfentanil (mg)	1233 (955–1533)	1189 (1015–1545)
Sufentanil (μg)	0 (0–0)	0 (0–0)
First postoperative concentration of CK-MB (U L^{-1})	59.5 (40.0–96.5)	58.0 (42.0–86.0)

a difference of 3% of ventilation time in the critical ventilation zone, based on findings in a previous study and an estimated baseline standard deviation of 2.5% of ventilation time, with a Type I error of 5% and corrected for dropouts.[23]

Results

Subject characteristics

From May 20, 2017 to April 19, 2018, 712 patients were screened (Fig. 1). Of 220 randomised Subject, 109 were allocated to the automated group and 111 to the conventional group. Baseline characteristics and dosages of peri- and postoperative i.v. sedative and analgesic medications were similar between the study groups (Table 2; Supplementary Table S1). Fully automated ventilation started 9 (4–21) min after arrival at the ICU, which was attributable to time needed to obtain the results of the first blood gas analysis required for programming of fully automated ventilation. Ventilator characteristics and initial arterial blood gas analyses are shown in Supplementary Tables S2 and S3 and Supplementary Figures S2–S4.

Primary outcome

Subjects in the fully automated group had a higher proportion of breaths in the optimal zone (Fig. 2), as illustrated by heat maps of ventilation in consecutive blocks of 15 min for the first 3 h of postoperative invasive ventilation (Fig. 3; Supplementary Figs S5–S8). Subjects in the automated group spent more time in optimal zones (55.2% [28.0]) compared with 25.5% (29.3%) for conventionally ventilated patients (MD: 29.7; 95% CI: 22.1–37.4; $P<0.001$; Table 3). Subjects in the automated group spent less time in the critical ventilation zone (0.0 [0.0–0.3]) compared with (0.3 [0.0–1.2]) for conventionally ventilated subjects (MD: 2.5% [95% CI: 0.8–4.1]; $P=0.003$) (Table 3). Accordingly, less time was spent in the acceptable zone (automated ventilation: 16.7% [16.7]) compared with 50.0

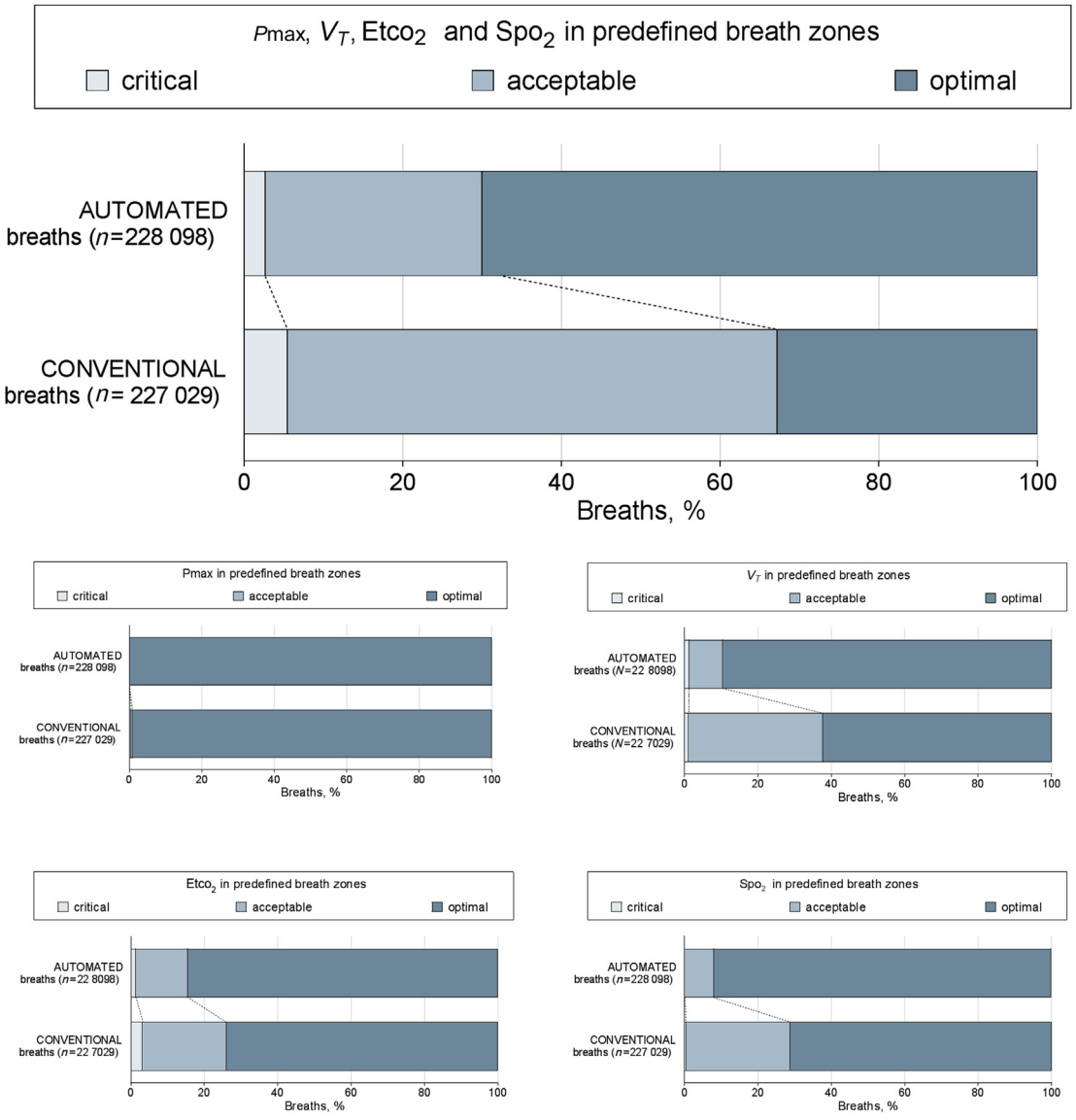

Fig 2. Percentage of breaths in predefined zones of ventilation.

(34.0%) for conventionally ventilated subjects (MD: −33.2 [95% CI: −40.4 to −26.1]; P<0.001). Reanalysis taking into account the absolute period of ventilation required for each subjects before liberation from the ventilator gave similar results (Supplementary Tables S4 and S6; Supplementary Fig. S9).

Secondary outcomes

The time until the first spontaneous breathing effort was shorter (Table 3; Supplementary Fig. S10) and the percentage of breaths with severe hypoxaemia was lower in the automated group. Duration of weaning and postoperative ventilation; the proportion of failed extubations; and developed postoperative pulmonary complications, ICU length of stay and readmission rates, and ICU and 30-day mortality were similar between automated and conventional ventilation groups (Supplementary Table S5).

Sensitivity and per-protocol analyses

Neither the per-protocol analysis (Supplementary Tables S5 and S6; Supplementary Figs S11 and S12) nor the sensitivity analysis (Supplementary Table S7) and *post hoc* analyses (Supplementary Table S8) altered the main findings. Differences in proportions of time spent in the ventilation zone between the automated group and the conventional group were similar in the two predefined subgroups (Supplementary Fig. S13).

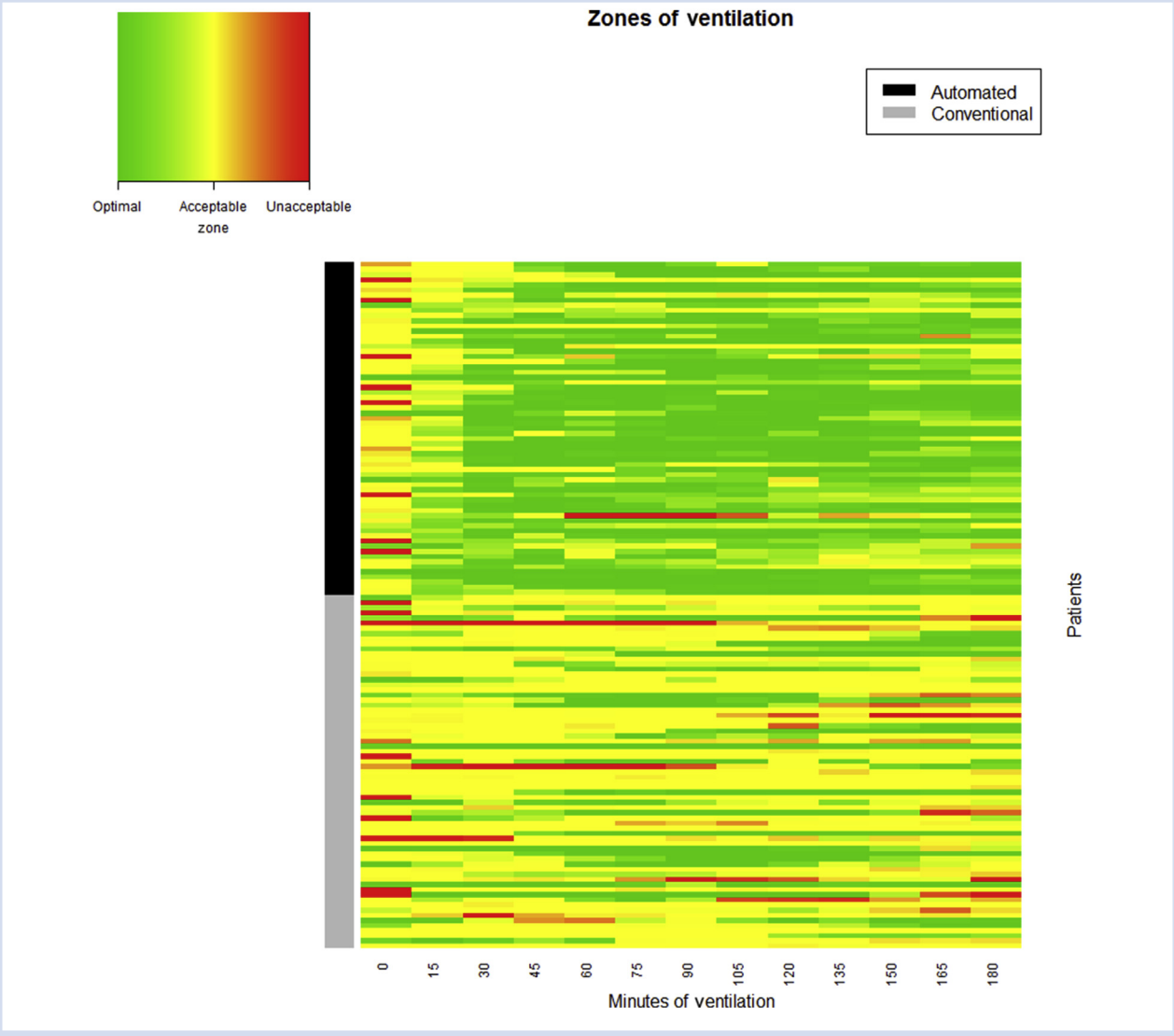

Fig 3. Heat map showing the ventilation zones every 15 minutes after randomisation. For the heat map construction, each breath was assigned to the corresponding ventilation zone and was given a numeric value as follows: 1 for a breath in the optimal zone, 2 for a breath in the acceptable zone, and 3 for a breath in the unacceptable zone. Then, all value of the breaths recorded within every 15 minutes were summarised using the mean of these values. The default colour gradient sets the lowest mean value to green (Optimal), the highest value to a bright red (Unacceptable), and mid-range values to yellow (Acceptable), with a corresponding transition between these extremes.

Discussion

We found that fully automated ventilation increased the time patients were exposed to optimal, lung-protective settings, whilst reducing the risk of injurious ventilation. Automated ventilation was more likely to prevent severe hypoxaemia and accelerated the time until spontaneous breathing.

To the best of our knowledge, this is the largest study to date that compares fully automated closed-loop ventilation with conventional ventilation in patients after cardiac surgery receiving postoperative ventilation. The predefined primary outcome, which is comparable with a previous study of automated ventilation,[23] reflects both efficacy and safety of ventilation, although the study population had little pre-existing pulmonary pathology. The study was designed to minimise bias by using concealed allocation, collection of breath-by-breath data, a modified intention-to-treat analysis, and a pragmatic protocol. Of note, the protocol was strictly followed by a team of experienced and board-certified ICU nurses and physicians, resulting in high adherence to the protective ventilation strategy in the conventional group.

The present study has important differences compared with previous investigations of INTELLiVENT-ASV in patients after cardiac surgery.[23,24] In the conventional group of the current study, V_T and P_{plat} were lower than in the previous investigation (median V_T <8 *vs* <10 ml kg^{-1} PBW; median P_{plat} <18 *vs* <21 cm H_2O),[23] and Spo_2 measurements were closer to contemporary targets of oxygenation (median <98% *vs* 99%). In addition, the present study used a stricter definition for

Table 3 Co-primary and secondary outcomes. *During the first 3 h of ventilation or until extubation and for at least 30 consecutive seconds. †During the first 3 h of ventilation or until extubation and reported according to the total number of breaths. ‡Defined as any re-intubation within 48 h after extubation and considering only patients who survived and did not undergo a re-sternotomy during this time. ¶Time from ICU admission until first successful extubation. §Time from stopping sedatives until successful extubation. ||Time from ICU admission until ≥5 consecutive spontaneous breaths. #During the first 72 h after ICU discharge. **When the measured Spo_2 had a quality index >50%. ††Effect estimate is mean difference. ‡‡Effect estimate is risk ratio. ¶¶Effect estimate is hazard ratio. §§One patient died the second day because of ventricular fibrillation as a result of cardiac ischaemia (postoperative coronary artery bypass graft failure); one patient died the second day as a result of an anastomotic rupture after aortic surgery; one patient died the fourth day because of a cardiac tamponade that occurred 3 days after extubation. ||||As no event was observed in one group, the effect estimate was not calculated (infinite in the upper limit). ##98.33% Bonferroni-corrected confidence intervals and P-values adjusted for multiplicity according to Benjamini–Hochberg are (i) percentage of time in critical zone: −2.5 (−4.5 to −0.5), 0.003; (ii) percentage of time in acceptable zone: −33.2 (−42.0 to −24.5), <0.001; and (iii) percentage of time in optimal zone: 29.7 (20.4–39.1), <0.001.

	Fully automated ventilation (n=109)	Conventional ventilation (n=111)	Effect estimate (95% CI)	P-value
Co-primary outcomes				
Percentage of time in the optimal zone*	55.2 (28.0)	25.5 (29.3)	29.7 (22.1–37.4)††,##	<0.001##
Median (IQR)	61.2 (32.4–78.9)	15.3 (0.0–49.0)		
Percentage of time in the acceptable zone*	16.7 (16.7)	50.0 (34.0)	−33.2 (−40.4 to −26.1)††,##	<0.001##
Median (IQR)	13.0 (4.6–22.9)	46.1 (19.0–83.6)		
Percentage of time in the critical zone*	0.5 (2.9)	3.0 (8.3)	−2.5 (−4.1 to −0.8)††,##	0.003##
Median (IQR)	0.0 (0.0–0.3)	0.3 (0.0–1.2)		
Secondary outcomes				
Percentage of breaths in the optimal zone†	159 643/228 098 (70.0)	74 537/227 021 (32.8)	2.20 (2.18–2.21)‡‡	<0.01
Percentage of breaths in the acceptable zone†	62 359/228 098 (27.3)	140 000/227 021 (61.7)	0.46 (0.46–0.47)‡‡	<0.01
Percentage of breaths in the critical zone†	6096/228 098 (2.7)	12 484/227 021 (5.5)	0.64 (0.63–0.65)‡‡	<0.01
Time until spontaneous breathing (min)||	164.0 (103.4)	211.7 (169.5)	1.38 (1.05–1.83)¶¶	0.02
Median (IQR)	142 (90–219)	162 (114–260)		
Duration of weaning (min)§	222.7 (328.2	265.7 (425.4	1.16 (0.88–1.53)¶¶	0.29
Median (IQR)	136 (73–241)	157 (75–323)		
Duration of ventilation (min)¶	448.3 (1085.2)	430.5 (457.2)	1.17 (0.89–1.54)¶¶	0.26
Median (IQR)	279 (195–412)	304 (204–477)		
Proportion of failed extubations‡	2/103 (1.9)	2/105 (1.9)	1.01 (0.40–2.71)‡‡	0.99
Incidence of postoperative pulmonary complications	87/109 (79.8)	96/111 (86.5)	0.80 (0.59–1.09)‡‡	0.18
Pneumonia	7/109 (6.4)	7/111 (6.3)	1.01 (0.59–1.73)‡‡	0.97
Pneumothorax	7/109 (6.4)	6/111 (5.4)	1.09 (0.65–1.84)‡‡	0.75
Atelectasis	87/109 (79.8)	95/111 (85.6)	0.82 (0.60–1.13)‡‡	0.25
ICU length of stay (days)	0.7 (1.0)	0.7 (0.7)	−0.0 (−0.2 to 0.2)††	0.96
Median (IQR)	0.3 (0.3–0.6)	0.4 (0.3–0.7)		
ICU readmissions#	2/109 (1.8)	4/111 (3.6)	0.67 (0.21–2.08)‡‡	0.68
Mortality				
ICU	3/109 (2.8)§§	0/111 (0.0)	—||||	0.12||||
30 days	3/109 (2.8)§§	0/111 (0.0)	—||||	0.08||||
Percentage of breaths with Spo_2 <85%†,**	116/232 211 (0.0)	807/252 244 (0.3)	0.26 (0.22–0.31)‡‡	<0.01

optimal ventilation. Indeed, in two previous studies,[23,24] V_T $\leq$10 ml kg^{-1} PBW was counted as optimal, whilst in the present study V_T $\leq$8 ml kg^{-1} PBW counted as optimal. These differences explain why the reported proportion of time in the optimal zone was lower than in a previous study.[23]

Even though the absolute MD in the critical zone of −2.5% seems small in this study, a much larger difference can be expected in settings with less resources, less staff, and resource-poor training facilities. Notably, we found a large MD in the optimal zone of 27.2%. This study shows that INTELLiVENT-ASV results in ventilation with a lower V_T, slightly higher PEEP, and a lower driving pressure compared with ventilation titrated by ICU nurses and doctors in an experienced specialist centre. Although evidence for benefit of ventilation with a lower V_T and a lower driving pressure is most convincing in patients with acute respiratory distress syndrome (ARDS),[16,28] there is increasing evidence for benefit of ventilation with a lower V_T or a lower driving pressure in patients not having ARDS.[29–32] Even during intraoperative ventilation, use of a lower V_T or a lower driving pressure has been found to be beneficial,[33–35] as was a high PEEP during postoperative ventilation in hypoxaemic cardiac surgery patients.[2]

Costs related to ICU patients are largely driven by costs pertaining to mechanically ventilated patients. Transforming the knowledge about protective ventilation into clinical practice is extremely challenging, but frequently time consuming and thus costly, which may result in inadequate and unsafe ventilatory support.[15,36–38] Discrepancies between demand and supply are expected to become more common because of an ageing population and increasing severity of illness in patients.[39,40] In addition, pandemics can put a huge strain on critical care resources, when systems have to struggle to provide high-quality care for a surge of critically ill patients in need of invasive ventilation. Fully automated ventilation modes could serve as a potential solution at minimal extra cost, whilst offering the potential to reduce the number of interactions with the ventilator by bedside caregivers.[20,22,25,26] However, future studies are needed to determine the cost-effectiveness of fully automated ventilation for general ICU populations in resource-rich and resource-poor settings.

Our study has several limitations. Blinding was not possible because of the nature of intervention. The primary objective of this study was to determine the efficacy and safety of INTELLiVENT-ASV when compared with ventilation titrated by ICU nurses and doctors. The use of surrogate endpoints may not necessarily translate into better clinical outcomes. Future randomised clinical trials of this fully automated mode of ventilation need to explore patient-centred outcomes. Caution is needed when extrapolating the results to other patient categories as the current study included a homogeneous cohort of only patients with minimal pre-existing pulmonary pathology who required postoperative mechanical ventilation for a relatively short period of time. Nonetheless, previous studies demonstrated that INTELLiVENT-ASV was safe and resulted in similar favourable improvements compared with conventional modes in critically ill patients with ARDS, COPD, or brain injury.[18,19,21,22,25–27] Also, as in previous studies, our study included haemodynamically stable patients.[20,23,24] Haemodynamic instability may interact unfavourably with automated ventilation software, because unstable patients with low cardiac output frequently have low Et_{CO_2} and Sp_{O_2} for haemodynamic reasons. In turn, these parameters may be 'misinterpreted' by the ventilator as a need for increase of minute ventilation and PEEP. Notably, in a previous study, the fully automated mode we tested performed similarly in fast-track cardiac surgery patients who were excluded in our study.[20] The plateau pressure was used as a surrogate measure for alveolar distending pressure to calculate the driving pressure and mechanical power. Whilst a direct measurement could have improved the accuracy of measurement, this was impractical in our study. Although the intention was to start the intervention as soon as the patient was admitted to the ICU, it was delayed until the results of the first blood gas analysis were available. However, the vast majority of patients commenced automated ventilation within 10 min after arrival in the ICU.

Conclusions

In this cohort of haemodynamic stable post-cardiac surgery patients receiving postoperative invasive ventilation by a team of well-trained and experienced ICU nurses and doctors, fully automated ventilation resulted in more likelihood of receiving lung-protective ventilation, fewer episodes of severe hypoxaemia, and more rapid return to spontaneous breathing. This study was not designed to evaluate other, more important patient-centred endpoints. Future studies should address whether fully automated ventilation is cost-effective in resource-rich and resource-poor settings.

Authors' contributions

Study conception: all authors
Study design: AJRDB, ASN, MJS, AJGHB
Data acquisition/interpretation: all authors
Statistical analysis: AJRDB, ASN, MJS, AJGHB
Administrative, technical, or material support: AJRDB, ASN, MJS, AJGHB
Supervision: ASN, MJS, AJGHB
Drafting/final approval of paper: all authors

Declarations of interest

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Appendix A. Supplementary data

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