AVAS trial

Automated control of mechanical ventilation during general anaesthesia

A bicentric prospective observational trial

Study protocol

General information

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Study team

    I.   **Kiel**

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    II.   **St. Pölten**

Univ.-Prof. Dr. Christoph Hörmann (principal investigator)

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Summary

Title	Prospective, bicentric observational study to assess a novel system for automated control of mechanical ventilation (SmartCare/AVent) during general anesthesia
Short title	AVAS-trial
Indication	Patients under general anesthesia
Design	Prospective observational trial
Primary endpoint	• Number of adverse events
Secondary endpoints	• Number of normoventilated, hypoventilated and hyperventilated patients. • Time period between switch from control to assisted ventilation and achievement of stable assisted ventilation of the patient • Proportion of time within the target zones for tidal volume and $PetCO_2$ as individually set up for each patient by the user • Number of alarms (anesthesia machine, SmartCare/AVent) • Frequency distribution of tidal volume, inspiratory pressure, inspiration time, expiration time and $PetCO_2$.
Target population	**Inclusion criteria** • Elective surgery of the upper limb, lower limb or, peripheral vascular surgery in general anesthesia without any additional regional anesthesia technique • ASA I, II or III • Age ≥ 18 years • Written consent of the patient for study participation **Exclusion criteria** • Mild, moderate or severe acute respiratory distress syndrome (ARDS) • Known chronic obstructive pulmonary disease Gold stage III or higher • Two or more acute organ failures • Patient is pregnant
Sample size	n=100 (50 per center)
Intervention	All patients will be mechanically ventilated with a novel automated mechanical ventilation system called SmartCare/AVent
Length of study	Approximately 6 months
Sponsor	None
Registration	clinicaltrials.gov ID NCT02644005

Rationale and background

Automated control of ventilator settings is a technology which is commonly used in ventilators used in the intensive care unit. Different systems (e. g. Intellivent-Adapative support ventilation [1], SmartCare/PS [2], neurally adjusted ventilator assist [3]) were developed and commercially distributed. Most of the systems are available since many years and were studied intensely [4-9].

During general anesthesia, the physician has to set-up the same ventilator settings as on an intensive care ventilator, however an automated control of ventilator settings is currently not available on anesthesia ventilators.

The SmartCare/AVent option is an automated control of ventilator settings (mechanical breathing frequency, inspiratory pressure, pressure support, inspiratory time, trigger sensitivity) which is available as an software option on a Zeus anesthesia ventilator (Dräger Medical, Lübeck, Germany). The system is CE-certified and currently no study investigating this device in a clinical study was published.

SmartCare/AVent controls the ventilator settings with the aim to keep a patient stable in a zone of respiratory comfort. This zone is adoptable by the user for each individual patient and consists of

- Lower limit for tidal volume
- Upper limit for tidal volume
- Lower limit for endtidal carbon dioxide concentration
- Upper limit for endtidal carbon dioxide concentration

Based on these limits, the system derives new ventilator settings every 15 seconds and is able to change the ventilator mode from controlled mechanical ventilation (pressure controlled ventilation) to assisted ventilation (pressure support ventilation). The physician has always the opportunity to change manually the ventilator settings or to stop the system. If SmartCare/AVent detects spontaneous breathing activity, the mechanical breathing frequency will automatically be decreased with the aim to increase the portion of spontaneous ventilation. The patient will be continuously monitored for possible instabilities. Last, the physician will be supported in the recovery process of the general anesthesia by supporting the induction of spontaneous breathing and by checking whether the respiratory drive of the patient is sufficient for extubation.

SmartCare/AVent may have the following beneficial effects:

- Improve efficacy and safety of mechanical ventilation during general anesthesia
- Increase the time period with assisted ventilation
- Decrease postoperative pulmonary complications
- Decrease the time needed for recovery of general anesthesia.

The purpose of this study is to describe the application of SmartCare/AVent in a clinical study and to assess its safety and efficacy.

Endpoints

Primary endpoint

- Frequency of adverse events (AE) defined as follows:
  - Severe Hypoventilation defined as minute volume lower than 40 ml/kg predicted body weight for longer than 5 minutes
  - Apnea for longer than 90 seconds

- Hyperventilation defined as endtidal partial carbon dioxide pressure ($PetCO_2$) lower than 5 mm Hg of the lower target setting for the SmartCare/AVent system for longer than 5 minutes. The responsible anesthesiologist defines a target for the arterial partial pressure of carbon dioxide ($PaCO_{2\_target}$) before the induction of the general anesthesia and sets up the corresponding endtidal CO_2-range in the automated ventilation system. 15 minutes after the beginning of the surgical procedure, an arterial blood gas analysis may be performed and the $PaCO_2$ will be measured.
- Hypoventilation defined as $PetCO_2$ higher than 5 mm Hg of the upper target setting for the SmartCare/AVent system for longer than 5 minutes
- Respiratory rate > 35 breaths per minute for longer than 5 minutes
- Any override or stop of the automated controlled ventilation settings by the anesthesiologist in charge if the settings are clinically not acceptable. The reasons for overriding or stopping the system will be noted.

Secondary endpoints

- Frequency of normoventilated, hypoventilated and hyperventilated patients. Patients will be classified as follows:
    - hypoventilated patient: $PaCO_2 > (PaCO_{2\_target}+5)$
    - hyperventilated patient: $PaCO_2 < (PaCO_{2\_target}-5)$
    - normoventilated patient: $(PaCO_{2\_target}-5) \leq PaCO_2 \leq PaCO_{2\_target}+5$
- Time period between switch from controlled ventilation to augmented ventilation and achievement of stable assisted ventilation of the patient
- Proportion of time within the target zones for tidal volume and $PetCO_2$ as individually set up for each patient by the user
- Frequency of alarms
- Frequency distribution of tidal volume, inspiratory pressure, inspiration time, expiration time and $PetCO_2$
- Number of re-intubations

Study description

Study design

Prospective, observational study in two University Hospitals:

I. University Medical Center Schleswig-Holstein, Campus Kiel
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    24105 Kiel
    Germany
II. Karl Landsteiner Privat University

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Department of Anesthesiology and Intensive Care Medicine
Propst-Führer-Straße 4
3100 St. Pölten
Austria

Sample size

100 patients (50 patients per center).

Expected duration of the study

6 months.

Target population

Inclusion criteria

All patients have to fulfill the following inclusion criteria:

- Elective surgery of the upper limb, lower limb or peripheral vascular surgery in general anesthesia without any additional regional anesthesia technique
- Patient is classified as ASA I, II or III
- Age ≥ 18 years
- Written consent of the patient for study participation

Exclusion criteria

Patients are excluded when the following criteria are fulfilled:

- Mild, moderate or severe acute respiratory distress syndrome (ARDS)[10]
- Known chronic obstructive pulmonary disease Gold stage III or higher
- Known neuro-muscular disease
- Two or more of the following acute organ failures
    - Hemodynamic instability: systolic blood pressure < 90 mm Hg, mean arterial pressure < 70 mm Hg or administration of any vasoactive drugs.
    - Acute renal failure: oliguria (urine output < 0.5 ml/kg/h for at least 2 hours despite of adequate management or creatinine increase > 0.5 mg/dl
    - Cerebral failure: loose of consciousness or encephalopathy
- Patient is pregnant.

Procedure of the study

Patients will be screened for possible study inclusion during the premedication visit.

Ethics committee

The study will be started after approval of the local ethics committees.

Study consent

Patients have to give written informed consent for study inclusion during the premedication visit.

Intervention

All patients will be ventilated with the SmartCare/AVent system available on the ZEUS anesthesia machine (Dräger Medical Lübeck, Germany). The SmartCare/AVent system does not control the inspired fraction of oxygen (F_IO_2) and positive end-expiratory pressure (PEEP). Therefore, the user has to set up both settings during the whole general anesthesia with the aim to reach SpO_2 greater than 95%.

Anesthesia will be performed by a physician of the study team who has been trained in using the SmartCare/AVent system. The physician can overrule or stop the system if this is necessary for patient safety. Reason for stopping or overruling will be documented.

Two different study scenarios are possible (according to the surgical procedure):

I. Early spontaneous breathing: Patient is allowed to breathe spontaneously immediately after induction of the general anesthesia.
II. Controlled mechanical ventilation: Patients will be ventilated in a controlled ventilation mode as long as needed for the surgical procedure. Then, spontaneous breathing will be allowed as soon as possible.

The study will proceed as follows:

I. Early spontaneous breathing

- Check of the anesthesia machine
- Set up of the individual alarm settings
- Set up of the SmartCare/AVent system:
    o level of ventilation, airway and lung mechanics as clinically indicated
    o phase: augmented ventilation
- Preoxygenation of the patient with an F_IO_2= 1 for at least 3 minutes
- Induction of the general anesthesia with an opioid (remifentanile, fentanyle or sufentanile) and propofol
- Hand bagging
- Insertion of the laryngeal mask or endotracheal tube
- Hand bagging while checking for significant leakage (laryngeal mask) and correction if needed
- Continuous infusion of remifentanile and propofol or administration of sevoflurane
- Start of SmartCare/AVent
- Insertion and position check of a gastric tube (if clinically indicated)
- Arterial blood gas analysis 15 minutes after the begin of the surgical procedure (if clinically indicated)

- Stop of the continuous infusion of remifentanile and propofol (or sevoflurane) immediately after the end of the surgical procedure and switch the SmartCare/AVent system to "recovery"

II. Controlled mechanical ventilation

- Check of the anaesthesia machine
- Set up of the individual alarm settings
- Set up of the SmartCare/AVent system
  - level of ventilation, airway and lung mechanics as clinically indicated
  - phase: controlled ventilation
- Preoxygenation of the patient with an $F_IO_2 = 1$ for at least 3 minutes
- Induction of the general anaesthesia with an opioid (remifentanile, fentanyle or sufentanile) and propofol
- Hand bagging
- Administration of muscle relaxant agent (rocuronium, cis-atracurium or succinylcholine) if needed
- Start of train-of-four (TOF) measurement (every 10 minutes)
- Insertion of the laryngeal mask or endotracheal tube
- Hand bagging while checking for significant leakage and correction if needed
- Continuous infusion of remifentanile and propofol or administration of sevoflurane
- Start of SmartCare/AVent
- Insertion and position check of a gastric tube (if clinically indicated)
- Arterial blood gas analysis 15 minutes after the begin of the surgical procedure (if clinically indicated)
- If TOF $\geq$ 2 stepwise decrease of remifentanile and propofol (or sevoflurane) with the aim to allow spontaneous breathing activity and switch the SmartCare/AVent system to "Augmented Ventilation"
- If no spontaneous breaths will be detected during 20 minutes the SmartCare/AVent system will be switched to "Encourage Spontaneous Breathing"
- Stop of the continuous infusion of remifentanile and propofol (or sevoflurane) immediately after the end of the surgical procedure and switch the SmartCare/AVent system to "Recovery"

Extubation

Readiness for extubation is given when SmartCare/AVent proposes separation from the ventilator.

Extubation will be performed when the following criteria are satisfied:

- Patient is awake and cooperative
- Sufficient airway protection or the Glasgow Coma Scale (GCS) >8
- No surgical contraindication.

After extubation, the patients will be monitored for at least 5 minutes in the operating room (OR).

End of study

The study period ends with the initiation of the patients' transfer from the OR to the recovery room.

Data recording

Beginning with the time of the study period all available data from the ventilator will be recorded via the MEDIBUS interface. In detail, flow, pressure and CO_2 values will be stored every 8 ms ("fast data"), all ventilator settings, measurements and alarms will be stored at least every second ("slow data"). All SmartCare/AVent patient session journal files will be systematically stored. Heart rate, SpO_2 and arterial blood pressures will be recorded at least every 5 minutes. In patients with a gastric tube, esophageal pressure swings will be recorded continuously ("fast data") until extubation. Data will be pseudonymized and then stored in a secured web space.

End-point determination

The end-points of the study are evaluated using the recorded and protocolled data of the study team only during mechanical ventilation with activated SVC.Ethical and legal aspects

In this clinical study, a novel system for automated control of mechanical ventilation will be examined. The system adapts ventilator settings according to the actual clinical situation which may lead to a shorter time period of controlled ventilation. There is no increased risk for the studied patients. SmartCare/AVent bases on well-known and established ventilator modes. In case of a technical breakdown of SmartCare/AVent, the anesthesia ventilator will continue its work. During the whole study period, a specially trained physician of the study team is at the patient in the OR and conducts the study. He monitors the patient and SmartCare/AVent and is able to stop the system at any time.

Additional examinations

None.

Medical device

The SmartCare/AVent option and the anesthesia ventilator Zeus used in this study is CE-certified. A copy of the CE-certificate is available as appendix of this experimental protocol.

Patient information and informed consent

The study team (study nurses and study physicians) will screen consecutively for eligible patients the day before surgery. Possible study candidates will be informed about the study in detail and asked to give consent for study participation.

Patient assurance

All medical devices used in this study are CE-certified. Therefore, a patient assurance is not needed.

Rules for early termination of the study

During each treatment of a patient in this study, the investigator is enabled to stop the study procedure when the ventilator settings controlled by the SmartCare/AVent system are clinically not appropriate or in case of a technical failure of the SmartCare/AVent system.

The study will be terminated if the study procedure was stopped by the investigator (as described above) in 5 consecutive patients.

Statistical analysis

Descriptive statistical analyses (mean ± standard deviation, median and 95% confidence interval where appropriate) will be used.

References

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3. **Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, Gottfried SB, Lindstrom L**: Neural control of mechanical ventilation in respiratory failure. Nature medicine 1999;5:1433-1436.
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Appendix

1. **Arnal JM, Wysocki M, Novotni D, Demory D, Lopez R, Donati S, Granier I, Corno G, Durand-Gasselin J**: Safety and efficacy of a fully closed-loop control ventilation (IntelliVent-ASV(R)) in sedated ICU patients with acute respiratory failure: a prospective randomized crossover study. Intensive Care Med 2012;38:781-787.
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