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**

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Dr. med. Georg Miestinger (investigator)

Summary

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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 (PetCO₂) 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 (PaCO₂_target) before the induction of the general anesthesia and sets up the corresponding endtidal CO₂-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 PaCO₂ will be measured.

Hypoventilation defined as PetCO₂ 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: PaCO₂ > (PaCO₂_target+5)
  - hyperventilated patient: PaCO₂ < (PaCO₂_target-5)
  - normoventilated patient: (PaCO₂_target-5) ≤ PaCO₂ ≤ PaCO₂_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 PetCO₂ 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 PetCO₂

- Number of re-intubations

Study description

Study design

Prospective, observational study in two University Hospitals:

I. University Medical Center Schleswig-Holstein, Campus Kiel
   Department of Anesthesiology and Intensive Care Medicine
   Arnold-Heller-Str. 3, Haus 12
   24105 Kiel
   Germany

II. Karl Landsteiner Privat University
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\textsubscript{I}O\textsubscript{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\textsubscript{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:
  - level of ventilation, airway and lung mechanics as clinically indicated
  - phase: augmented ventilation
- Preoxygenation of the patient with an F\textsubscript{I}O\textsubscript{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 remifentanil 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
  o level of ventilation, airway and lung mechanics as clinically indicated
  o phase: controlled ventilation
• Preoxygenation of the patient with an F\textsubscript{\text{1}}O\textsubscript{\text{2}}= 1 for at least 3 minutes
• Induction of the general anaesthesia with an opioid (remifentanil, fentanyl or sufentanil) 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 remifentanil 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 remifentanil 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 remifentanil 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) \geq 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 CO₂ 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, SpO₂ 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
Appendix


