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Automated control of mechanical ventilation during general anaesthesia: study protocol of a bicentric observational study (AVAS)

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ABSTRACT

Introduction Automated control of mechanical ventilation during general anaesthesia is not common. A novel system for automated control of most of the ventilator settings was designed and is available on an anaesthesia machine.

Methods and analysis The 'Automated control of mechanical ventilation during general anesthesia study' (AVAS) is an international investigator-initiated bicentric observational study designed to examine safety and efficacy of the system during general anaesthesia. The system controls mechanical breathing frequency, inspiratory pressure, pressure support, inspiratory time and trigger sensitivity with the aim to keep a patient stable in user adoptable target zones. Adult patients, who are classified as American Society of Anesthesiologists physical status I, II or III, scheduled for elective surgery of the upper or lower limb or for peripheral vascular surgery in general anaesthesia without any additional regional anaesthesia technique and who gave written consent for study participation are eligible for study inclusion. Primary endpoint of the study is the frequency of specifically defined adverse events. Secondary endpoints are frequency of normoventilation, hypoventilation and hyperventilation, the time period between switch from controlled ventilation to assisted ventilation, achievement of stable assisted ventilation of the patient, proportion of time within the target zone for tidal volume, end-tidal partial pressure of carbon dioxide as individually set up for each patient by the user, frequency of alarms, frequency distribution of tidal volume, inspiratory pressure, inspiration time, expiration time, end-tidal partial pressure of carbon dioxide and the number of re-intubations.

Ethics and dissemination AVAS will be the first clinical study investigating a novel automated system for the control of mechanical ventilation on an anaesthesia machine. The study was approved by the ethics committees of both participating study sites. In case that safety and efficacy are acceptable, a randomised controlled trial comparing the novel system with the usual practice may be warranted.

Trial registration DRKS DRKS00011025, registered 12 October 2016; clinicaltrials.gov ID. NCT02644005, registered 30 December 2015.

Strengths and limitations of this study

► Safety and efficacy of a novel system for the automated control of mechanical ventilation on an anaesthesia machine as well as feasibility of early assisted ventilation during general anaesthesia in terms of a proof-of-concept approach will be assessed using an observational study design.

► In case that safety and efficacy are acceptable, a randomised controlled trial comparing the novel system with the usual practice may be warranted. For the design of such a study, the results and the experience obtained with the 'Automated control of mechanical ventilation during general anesthesia study' (AVAS) would be of benefit.

► The clinical value of the AVAS will be limited due to the observational study design.

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introduced in ventilators used in the intensive care unit (ICU). Different systems (eg, Intellivent-Adaptive Support Ventilation,[1] SmartCare/PS[2] and Neurally Adjusted Ventilator Assist)[3] were developed and commercially distributed. When comparing the performance of automated systems with the clinical routine, it has been shown that automated systems are able to keep a patient in a specified target zone (TZ) for a significantly higher percentage of time than clinicians.[4 5] Several randomised controlled trials investigated the effect of automated systems on ventilation time in patients who were weaned from mechanical ventilation. In some studies no significant differences in ventilation times were found,[6–11] whereas other studies revealed that automated systems shortened the ventilation time[12–18] when compared with weaning protocols or usual care.

During general anaesthesia, the physician has to set-up the same ventilator settings as on an intensive care ventilator. However, an

INTRODUCTION

Automated control of mechanical ventilation is a technology which has been

automated control of ventilator settings is currently not available on anaesthesia machines. A novel system called smart ventilation control (SVC) was designed. SVC automatically controls the mechanical breathing frequency, inspiratory time, inspiratory pressure, pressure support and triggers sensitivity and was implemented on an anaesthesia machine (Zeus Infinity Empowered, Drägerwerk AG & Co. KGAa, Lübeck, Germany). The system is designed to adapt the ventilatory settings to keep a patient stable in a TZ. Furthermore, spontaneous breathing activity will be supported as soon as possible. In this paper we describe the design of the first clinical study that will be performed with SVC during general anaesthesia.

METHODS AND ANALYSIS

The '*Automated control of mechanical ventilation during general anesthesia study*' (AVAS) is an international investigator-initiated bicentric observational study investigating the application of SVC during general anaesthesia. The study was approved by the Ethics Committee of the Medical Faculty of the Christian-Albrechts-University of Kiel, Germany (A154/14) by the Ethics Committee of the county Niederösterreich (GS-1-EK-3/118–2016) and is registered at clinicaltrials.gov (NCT02644005). The study protocol is available as online supplementary appendix. The main objective of this study is to describe the application of SVC and to assess its safety and efficacy.

Description of the system

SVC controls automatically the following ventilator settings:
► Mechanical breathing frequency (f_{mech})
► Inspiratory pressure (P_{insp})
► Pressure support (PS)
► Inspiratory time (T_I)
► Trigger sensitivity (T_S)

Inspired fraction of oxygen and positive end-expiratory pressure are not controlled automatically. SVC adjusts the ventilator settings with the aim to keep a patient stable in a TZ. Numerous predefined TZs exist that can be set according to the current therapeutic situation. All TZs can be customised by the user for each individual patient and consist of upper and lower limits for tidal volume (V_T) and for the end-tidal partial pressure of carbon dioxide ($P_{et}CO_2$). Based on these limits, the system classifies the current quality of ventilation, called classification of ventilation, and derives new ventilator settings accordingly. This is done every 15 s. The physician always has the opportunity to change the ventilator settings manually or to stop the system. If SVC detects spontaneous breathing activity, the mechanical breathing frequency is decreased automatically with the aim to increase the portion of spontaneous ventilation adequately if 'augmented ventilation' is activated. In case that 'encourage spontaneous breathing' is activated, SVC will automatically change the ventilator mode from controlled mechanical ventilation (pressure controlled ventilation) to assisted ventilation (pressure support ventilation) if $P_{et}CO_2$ is classified as mild hypoventilation. The patient is continuously monitored for possible instabilities. Lastly, the physician is supported in the recovery process of general anaesthesia by supporting the induction of spontaneous breathing and by checking whether the respiratory drive of the patient is sufficient for extubation.

SVC is available as a software option on Zeus Infinity Empowered anaesthesia machines (Drägerwerk AG & Co. KGAa, Lübeck, Germany) and is approved as a medical product according to 93/42/European Economic Community (EEC).

Patient screening

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.

Inclusion and exclusion criteria

The following inclusion criteria will be used:
► Elective surgery of the upper limb, lower limb or peripheral vascular surgery in general anaesthesia without any additional regional anaesthesia technique.
► Patient is classified as American Society of Anesthesiologists physical status I, II or III.
► Age ≥18 years.
► Written consent of the patient for study participation.

Patients will be excluded when meeting one or more of the following exclusion criteria:
► Mild, moderate or severe acute respiratory distress syndrome.[19]
► Known chronic obstructive pulmonary disease Gold stage III or higher.[20]
► Known neuro-muscular disease.
► Patient is pregnant.
► Two or more of the following acute organ failures or haemodynamic instability defined as systolic blood pressure <90 mm Hg, mean arterial pressure <70 mm Hg or administration of any vasoactive drugs or acute renal failure defined as oliguria, that is, urine output <0.5 mL/kg/hour for at least 2 hours despite of adequate management or creatinine increase >0.5 mg/dL or cerebral failure: loss of consciousness or encephalopathy.

STUDY PROCEDURE

All patients will be ventilated with SVC. As SVC does not control the inspired fraction of oxygen (F_IO_2) and positive end-expiratory pressure, the user will have to set up both of these settings during the whole general anaesthesia with the aim to reach a peripheral saturation of oxygen (SpO_2) >95%.

Anaesthesia will be performed by a physician of the study team who has been trained in using SVC. The physician can overrule or stop the system at any time if this is necessary
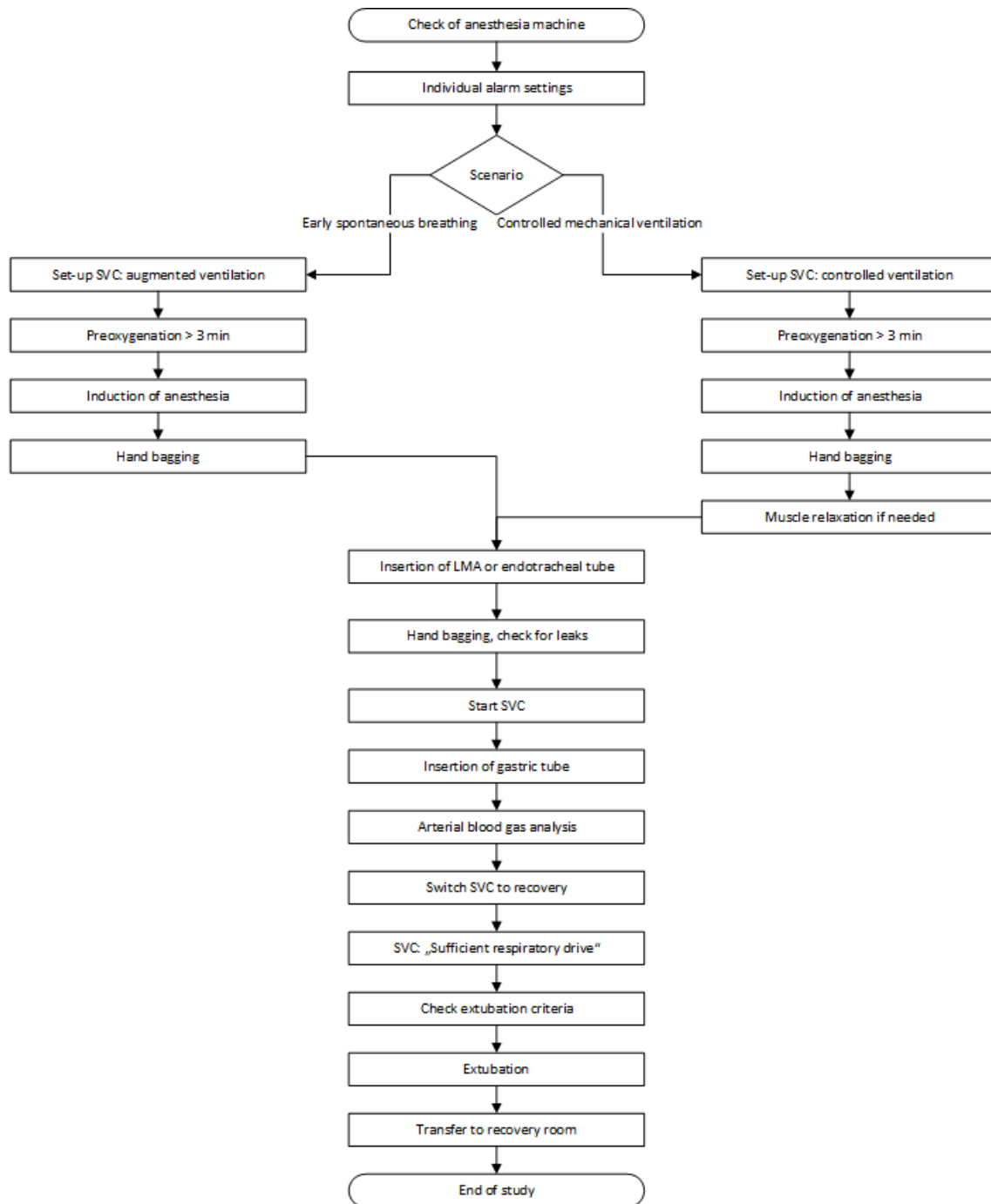
Figure 1 Flowchart of study procedure. LMA, laryngeal mask; SVC, smart vent control.

for patient safety. Reasons for stopping or overruling will be documented. Insertion of a tube for gastric decompression is part of our routine clinical practice in endotracheally intubated patients. For this study, we will use a gastric tube for decompression that is additionally equipped with an oesophageal balloon for assessment of oesophageal pressure (Nutrivent, Sidam, Mirandola, Italy).

Two different study scenarios are possible according to the surgical procedure (figure 1): (i) *Early spontaneous breathing*: Patient is allowed to breathe spontaneously immediately after induction of the general anaesthesia. (ii) *Controlled mechanical ventilation*: Patient 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
► Checking of the anaesthesia machine.
► Setting of the individual alarm settings.
► Setting of SVC:
  ► level of ventilation, airway and lung mechanics as clinically indicated
  ► ventilation regime: augmented ventilation.

- ► Preoxygenation of the patient with an $F_IO_2=1$ for at least 3 min.
- ► Induction of the general anaesthesia with an opioid (remifentanile, fentanyle or sufentanile) and propofol.
- ► Hand bagging.
- ► Insertion of the laryngeal mask or the endotracheal tube.
- ► Hand bagging while checking for significant leakage (laryngeal mask) and doing correction if needed.
- ► Continuous infusion of remifentanile and propofol or administration of sevoflurane.
- ► Start of SVC.
- ► Insertion and position check of a gastric tube (if clinically indicated).
- ► Arterial blood gas analysis 15 min after the beginning of the surgical procedure (if clinically indicated).
- ► Stopping of the continuous infusion of remifentanile and propofol (or sevoflurane) immediately after the end of the surgical procedure and switch SVC ventilation regime to 'Recovery'.

II. Controlled mechanical ventilation

- ► Checking of the anaesthesia machine.
- ► Setting of the individual alarm settings.
- ► Setting of SVC
  - ► level of ventilation, airway and lung mechanics as clinically indicated
  - ► ventilation regime: controlled ventilation.
- ► Preoxygenation of the patient with an $F_IO_2=1$ for at least 3 min.
- ► 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 min).
- ► Insertion of the laryngeal mask or endotracheal tube.
- ► Hand bagging while checking for significant leakage and doing correction if needed.
- ► Continuous infusion of remifentanile and propofol or administration of sevoflurane.
- ► Start of SVC.
- ► Insertion and position check of a gastric tube (if clinically indicated).
- ► Arterial blood gas analysis 15 min after the begin of the surgical procedure (if clinically indicated).
- ► If TOF ≥2 stepwise decrease of remifentanile and propofol (or sevoflurane) with the aim to allow spontaneous breathing activity and switch the SVC system to 'Augmented Ventilation'.
- ► If no spontaneous breaths are detected during 20 min, the SVC 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 SVC ventilation regime to 'Recovery'.

EXTUBATION

Readiness for extubation is given when SVC 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 >8 and no surgical contraindication. After extubation, the patients will be monitored for at least 5 min in the operating room (OR). The study period ends with the initiation of the patients' transfer from the OR to the recovery room.

Study endpoints

Primary endpoint of the study is the frequency of AE defined as follows:

- ► Severe hypoventilation defined as minute volume <40 mL/kg predicted body weight for >5 min.
- ► Apnoea for >90 s.
- ► Hyperventilation defined as $P_{et}CO_2$<5 mm Hg of the lower target setting for SVC for >5 min. The responsible anesthesiologist defines a target for the arterial PaO_2 of carbon dioxide ($P_aCO_{2\_target}$) before the induction of the general anaesthesia and sets the corresponding end-tidal CO_2 range in the automated ventilation system. Fifteen minutes after the beginning of the surgical procedure, an arterial blood gas analysis may be performed and P_aCO_2 will be measured.
- ► Hypoventilation defined as $P_{et}CO_2$>5 mm Hg of the upper target setting for the SVC for >5 min.
- ► Respiratory rate >35 breaths per minute for >5 min.
- ► Any override or stop of the automated controlled ventilation settings by the anesthesiologist in charge if the settings are clinically not acceptable. Reasons for overriding or stopping the system will be noted.

Secondary endpoints are as follows:

- ► Frequency of normoventilated, hypoventilated and hyperventilated patients. Patients will be classified as follows:
  - ► Hypoventilated patient: $P_aCO_2 > (P_aCO_{2\_target} + 5$ mm Hg$)$.
  - ► Hyperventilated patient: $P_aCO_2 < (P_aCO_{2\_target} - 5$ mm Hg$)$.
  - ► Normoventilated patient: $(P_aCO_{2\_target} - 5$ mm Hg$) \leq P_aCO_2 \leq P_aCO_{2\_target} + 5$ mm Hg.
- ► Time period between the switch from controlled to assisted ventilation and achievement of stable assisted ventilation of the patient.
- ► Proportion of time within the TZ for V_T and $P_{et}CO_2$ as individually set up for each patient by the user.
- ► Frequency of alarms.
- ► Frequency distribution of V_T, P_{insp}, T_I, expiration time and $P_{et}CO_2$.
- ► Number of re-intubations.

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.

Data recording

After study inclusion the following demographic characteristics will be documented: patients' age, sex, height, weight, date and type of surgery. 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 expired CO_2 will be stored every 8 ms ('fast data'), and all ventilator settings, measurements and alarms will be stored at least every second ('slow data'). All SVC patient session journal files will be systematically stored. Heart rate, SpO_2 and arterial blood pressures will be recorded at least every 5 min. In patients with a gastric tube, oesophageal pressure swings will be recorded continuously ('fast data') until extubation. Data will be pseudonymised and then stored in a secured web space.

Rules for early termination of the study

During each treatment of a patient in this study, the investigator can stop the study procedure when the ventilator settings controlled by SVC are clinically not appropriate or in case of a technical failure of the SVC system. The study will be terminated if the study procedure is stopped by the investigator (as described above) in five consecutive patients.

Statistical considerations

We estimated a frequency of 3%–5% for the AE. Therefore, a sample size of n=100 patients seems reasonable. Descriptive statistical analyses (mean±SD, median and 95% CI where appropriate) will be used.

ETHICS AND DISSEMINATION

In contrast to conventional anaesthesia machines, automated control of mechanical ventilation is steadily increasing in ICU ventilators. The commercially available systems cover the control of one ventilator setting, that is the pressure support level during weaning (SmartCare/PS)[2], minute ventilation (mandatory minute ventilation,[21] adaptive support ventilation (ASV))[22–25] or even all ventilatory settings (Intellivent-ASV).[1] SVC provides an automated control of minute ventilation by adapting TI, f_{mech}, P_{insp} and PS and supports spontaneous breathing activity as soon as possible by decreasing f_{mech} and by switching between pressure controlled and pressure support ventilation. It has been shown that the suppression of spontaneous breathing activity contributes to ventilator-induced lung injury,[26] leads to ventilator-induced diaphragmatic dysfunction[27] and increases the risk of developing pneumonia when increasing ventilation time in ICU patients.[28] It is known that the induction of a general anaesthesia leads to a cranial movement of the diaphragm-provoking atelectasis.[29] Putensen et al showed nicely that the early use of assisted ventilation leads to recruitment of atelectatic lung regions and thereby improves lung mechanics and gas exchange in patients at high risk of developing lung injury.[30] Therefore, an automated system that supports assisted ventilation as early as possible may have beneficial effects like decreasing the frequency of pulmonary complications, the amount of anaesthesia and vasoactive drugs and recovery time. However, in this study with the first SVC use in patients, we focus on the safety and efficacy of the system and assess the feasibility of early assisted ventilation during general anaesthesia in terms of a proof-of-concept approach. In case that safety and efficacy are acceptable (ie, the study was not stopped per the early termination rule) in this study, a randomised controlled trial comparing SVC with the usual practice may be warranted. As spontaneous breathing may not be acceptable or possible during some surgical procedures (eg, neuromuscular blockade needed for the surgical procedure), we designed two different study scenarios (early spontaneous breathing and controlled mechanical ventilation).

Regarding the study design one may argue that a prespecified list for overruling or stopping the system may be provided to the study physicians. Such a list may prohibit inaccurate overriding or stopping of SVC. From our point of view, it is the responsibility and the ethical duty of the study physician to override the ventilatory settings provided by SVC or even stop SVC for any safety reason. Should a list of possible reasons for overruling or stopping be defined in the study protocol, the individual decision of the study physician might be limited or influenced. Therefore, we decided not to provide such a list. We plan to categorise reasons for overruling or stopping SVC after the completion of the whole study.

A three-step dissemination strategy is planned as follows: first, the study results will be presented at international anaesthesia conferences; second, the study will be published in a peer-reviewed journal and third, a multicentre randomised controlled study will be designed.

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