BMJ Open

Automated control of mechanical ventilation during general anesthesia – study protocol of a bicentric observational study (AVAS study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014742
Article Type:	Protocol
Date Submitted by the Author:	17-Oct-2016
Complete List of Authors:	Schädler, Dirk; University Medical Center Schleswig-Holstein, Campus Kiel, Department of Anesthesiology and Intensive Care Medicine Miestinger, Georg; University Hospital St. Pölten, Department of Anesthesiology and Intensive Care Medicine Becher, Tobias; University Medical Center Schleswig-Holstein, Campus Kiel, Department of Anesthesiology and Intensive Care Medicine Frerichs, Inéz; University Medical Center Schleswig-Holstein, Campus Kiel, Department of Anesthesiology and Intensive Care Medicine Weiler, Norbert; University Medical Center Schleswig-Holstein, Campus Kiel, Department of Anesthesiology and Intensive Care Medicine Hörmann, Christoph; University Hospital St. Pölten, Department of Anesthesiology and Intensive Care Medicine
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Respiratory medicine, Surgery, Patient-centred medicine
Keywords:	Adult anaesthesia < ANAESTHETICS, Adult surgery < SURGERY, Clinical trials < THERAPEUTICS

Automated control of mechanical ventilation during general anesthesia – study protocol of a bicentric observational study (AVAS study)

Dirk Schädler[1*] MD, dirk.schaedler@uksh.de

Georg Miestinger[2] MD, georg.miestinger@stpoelten.lknoe.at

Tobias Becher[1] MD, tobias.becher@uksh.de

Inéz Frerichs[1] MD, inez.frerichs@uksh.de

Norbert Weiler[1] MD, norbert.weiler@uksh.de

Christoph Hörmann[2] MD, christoph.hoermann@stpoelten.lknoe.at

[1]Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Arnold-Heller-Straße 3, Haus 12, 24105 Kiel, Germany.
[2]Department of Anesthesiology and Intensive Care Medicine, University Hospital St. Pölten, Propst-Führer-Straße 4, St. Pölten A-3100

*Corresponding author

Abstract

Introduction: Automated control of mechanical ventilation during general anesthesia is not common. A novel system for automated control of most of the ventilator settings was designed and is available on an anesthesia machine. The system is designed to support spontaneous breathing activity by decreasing mechanical breathing frequency and by switching from controlled to assisted ventilation immediately after its detection.

Methods and analysis: The AVAS study is an international investigator-initiated bicentric observational study designed to examine safety and efficacy of the system during general anesthesia. 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 anesthesia 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 augmented ventilation, achievement of stable assisted ventilation of the patient, proportion of time within the target zones 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 anesthesia machine. In case that safety and efficacy are acceptable, a randomized 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

Abstract word count: 299/350

Strengths and limitations of this study

- This will be the first clinical study investigating a novel automated system for the automated control of mechanical ventilation on an anesthesia machine.
- Safety and efficacy of the system as well as feasibility of early assisted ventilation during general anesthesia in terms of a proof-of-concept approach will be assessed.

Keywords

Closed-loop-control of mechanical ventilation, knowledge based system, spontaneous breathing, general anesthesia, automatic control of artificial ventilation.

Introduction

Automated control of mechanical ventilation is a technology which is commonly applied in ventilators used in the intensive care unit (ICU). Different systems (e. g. Intellivent - Adaptive Support Ventilation [1], SmartCare/PS [2], Neurally Adjusted Ventilator Assist [3]) were developed and commercially distributed. Most of the systems are available for many years and were studied extensively [1 4-19].

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 machines. A novel system called Smart Vent Control (SVC) was designed to automatically control the following ventilator settings:

- Mechanical breathing frequency (f_{mech})
- Inspiratory pressure (P_{insp})
- Pressure support (PS)
- Inspiratory time (T_I)
- Trigger sensitivity (T_S).

SVC adjusts the ventilator settings with the aim to keep a patient stable in a target zone (TZ). Numerous predefined TZs exist that can be set according to the current therapeutic situation. All TZs are adoptable by the user for each individual patient and consist of upper and lower limits for tidal volume (V_T) and for the partial pressure of end-tidal carbon dioxide ($P_{et}CO_2$). Based on these limits, the system classifies the current quality of ventilation, called Classification of Ventilation (CoV), and derives new ventilator settings accordingly. This is done every 15 seconds. 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 this case, if sufficient spontaneous breathing activity is detected, SVC will automatically change the ventilator mode from controlled mechanical ventilation (pressure controlled ventilation, PCV) to assisted ventilation (pressure support ventilation, PSV). The patient is continuously monitored for possible instabilities. Lastly, the physician is supported in the recovery process of general anesthesia 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 anesthesia machines (Drägerwerk AG & Co. KGAa, Lübeck, Germany) and is approved as a medical product according to 93/42/European Economic Community (EEC). This medical device has not been investigated in a clinical trial yet. In this paper we describe the design of the first clinical study that will be performed with SVC during general anesthesia.

Methods and Analysis

The "**A**utomated control of mechanical **v**entilation during general **a**nesthesia **s**tudy (AVAS study) is an international investigator-initiated bicentric observational study investigating the application of SVC during general anesthesia. The study was approved by the Ethics Committee of the Medical Faculty of the Christian Albrechts University 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 main objective of this study is to describe the application of SVC and to assess its safety and efficacy.

Patient screening

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

- Planned elective surgery of the upper limb, lower limb or peripheral vascular surgery in general anesthesia
- Patient is classified as American Society of Anesthesiologists (ASA) 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 (ARDS) [20]
- Known chronic obstructive pulmonary disease Gold stage III or higher [21]
- Patient is pregnant
- Two or more of the following organ failures
    - Mild, moderate or severe ARDS
    - Hemodynamic instability defined as systolic blood pressure < 90 mm Hg, mean arterial pressure < 70 mmHg or administration of any vasoactive drugs

- Acute renal failure defined as oliguria, i.e. 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: loss of consciousness or encephalopathy.

Study procedure

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

Anesthesia 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 for patient safety. Reasons for stopping or overruling will be documented.

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 anesthesia, 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

- Check of the anesthesia 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 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 SVC
- Insertion and position check of a gastric tube (routine)
- Arterial blood gas analysis 15 minutes after the beginning of the surgical procedure (routine)
- 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”

II. Controlled mechanical ventilation

- Check of the anesthesia 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 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
- 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 SVC
- Insertion and position check of a gastric tube (routine)
- Arterial blood gas analysis 15 minutes after the begin of the surgical procedure (routine)
- 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 minutes, 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 (GCS) >8, no surgical

contraindication. After extubation, the patients will be monitored for at least 5 minutes 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 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 $P_{et}CO_2$ lower than 5 mm Hg of the lower target setting for SVC for longer than 5 minutes
- Hypoventilation defined as $P_{et}CO_2$ higher than 5 mm Hg of the upper target setting for the SVC 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. Reasons for overriding or stopping the system will be noted.

Secondary endpoints are:

- Frequency of normoventilated, hypoventilated and hyperventilated patients. The responsible anesthesiologist defines a target range for the arterial partial pressure of carbon dioxide ($P_aCO_{2\_target}$) before the induction of the general anesthesia and sets the corresponding end-tidal CO_2 range in the automated ventilation system. 15 minutes after the begin of the surgical procedure an arterial blood gas analysis will be performed and P_aCO_2 will be measured. Then 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) ≤ $P_aCO_2 \leq P_aCO_{2\_target} + 5$ mm Hg

- Time period between the switch from controlled to augmented ventilation and achievement of stable assisted ventilation of the patient
- Proportion of time within the target zones 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 data and the protocolled data of the study team.

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"), 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 minutes. Esophageal pressure swings will be recorded continuously ("fast data").

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 5 consecutive patients.

Statistical considerations

We estimated a frequency of 3 to 5 % for the adverse events. Therefore, a sample size of n=100 patients seems reasonable. Descriptive statistical analyses (mean ± standard deviation, median and 95% confidence interval where appropriate) will be used.

Ethics and dissemination

In contrast to conventional anesthesia machines, automated control of mechanical ventilation is steadily increasing in ICU ventilators. The commercially available systems cover the control of one ventilator setting, i.e. the pressure support level during weaning (SmartCare/PS)[2]), minute ventilation (mandatory minute ventilation, MMV[22], adaptive support ventilation, ASV [23-26]) or even all ventilatory settings (intellivent-ASV)[1]. SVC provides an automated control of minute ventilation by adapting T_I, 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 [27], leads to ventilator-induced diaphragmatic dysfunction [28] and increases the risk of developing pneumonia when increasing ventilation time in ICU patients [29]. It is known that the induction of a general anesthesia leads to a cranial movement of the diaphragm provoking atelectasis [30]. 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 [31]. Therefore, an automated system that supports assisted ventilation as early as possible may have many beneficial effects like decreasing the frequency of pulmonary complications, decreasing the amount of anesthesia drugs or vasoactive drugs and decreasing 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 anesthesia in terms of a proof-of-concept approach. In case that safety and efficacy are acceptable in this study, a randomized controlled trial comparing SVC with the usual practice may be warranted. As spontaneous breathing may not be acceptable or possible during some surgical procedures (e. g. neuromuscular blockade needed for the surgical procedure), we designed two different study scenarios (early spontaneous breathing and controlled mechanical ventilation).

References

1. Arnal JM, Wysocki M, Novotni D, et al. 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 medicine 2012;**38**(5):781-7 doi: 10.1007/s00134-012-2548-6[published Online First: Epub Date]|.

2. Dojat M, Brochard L, Lemaire F, Harf A. A knowledge-based system for assisted ventilation of patients in intensive care units. International journal of clinical monitoring and computing 1992;**9**(4):239-50

3. Sinderby C, Navalesi P, Beck J, et al. Neural control of mechanical ventilation in respiratory failure. Nature medicine 1999;**5**(12):1433-6 doi: 10.1038/71012[published Online First: Epub Date]|.

4. Burns KEA, Meade MO, Lessard MR, et al. Wean Earlier and Automatically with New Technology (the WEAN Study). A Multicenter, Pilot Randomized Controlled Trial. American journal of respiratory and critical care medicine 2013;**187**(11):1203-11 doi: 10.1164/rccm.201206-1026OC[published Online First: Epub Date]|.

5. Dongelmans DA, Schultz MJ. Adaptive support ventilation: an inappropriate mechanical ventilation strategy for acute respiratory distress syndrome? Anesthesiology 2010;**112**(5):1295; author reply 95-6 doi: 10.1097/ALN.0b013e3181d74f71

00000542-201005000-00051 [pii][published Online First: Epub Date]|.

6. Dongelmans DA, Veelo DP, Bindels A, et al. Determinants of tidal volumes with adaptive support ventilation: a multicenter observational study. Anesth Analg 2008;**107**(3):932-7 doi: 107/3/932 [pii]

10.1213/ane.0b013e31817f1dcf[published Online First: Epub Date]|.

7. Dongelmans DA, Veelo DP, Paulus F, et al. Weaning automation with adaptive support ventilation: a randomized controlled trial in cardiothoracic surgery patients. Anesth Analg 2009;**108**(2):565-71 doi: 108/2/565 [pii]

10.1213/ane.0b013e318190c49f[published Online First: Epub Date]|.

8. Hendrix H, Kaiser ME, Yusen RD, Merk J. A randomized trial of automated versus conventional protocol-driven weaning from mechanical ventilation following coronary artery bypass surgery. Eur J Cardiothorac Surg 2006;**29**(6):957-63

9. Holt SJ, Sanders RC, Thurman TL, Heulitt MJ. An evaluation of Automode, a computer-controlled ventilator mode, with the Siemens Servo 300A ventilator, using a porcine model. Respir Care 2001;**46**(1):26-36

10. Iotti GA, Polito A, Belliato M, et al. Adaptive support ventilation versus conventional ventilation for total ventilatory support in acute respiratory failure. Intensive care medicine 2010 doi: 10.1007/s00134-010-1917-2[published Online First: Epub Date]|.

11. Laubscher TP, Heinrichs W, Weiler N, Hartmann G, Brunner JX. An adaptive lung ventilation controller. IEEE Trans Biomed Eng 1994;**41**(1):51-9

12. Lellouche F, Mancebo J, Jolliet P, et al. A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. Am J Respir Crit Care Med 2006;**174**(8):894-900 doi: 10.1164/rccm.200511-1780OC[published Online First: Epub Date]|.

13. Petter AH, Chiolero RL, Cassina T, Chassot PG, Muller XM, Revelly JP. Automatic "respirator/weaning" with adaptive support ventilation: the effect on duration of endotracheal intubation and patient management. Anesth Analg 2003;**97**(6):1743-50

14. Roth H, Luecke T, Lansche G, Bender HJ, Quintel M. Effects of patient-triggered automatic switching between mandatory and supported ventilation in the postoperative weaning period. Intensive care medicine 2001;**27**(1):47-51

15. Schädler D, Engel C, Elke G, et al. Automatic control of pressure support for ventilator weaning in surgical intensive care patients. Am J Respir Crit Care Med 2012;**185**(6):637-44 doi: 10.1164/rccm.201106-1127OC[published Online First: Epub Date]|.

16. Sulzer CF, Chiolero R, Chassot PG, Mueller XM, Revelly JP. Adaptive support ventilation for fast tracheal extubation after cardiac surgery: a randomized controlled study. Anesthesiology 2001;**95**(6):1339-45

17. Tassaux D, Dalmas E, Gratadour P, Jolliet P. Patient-ventilator interactions during partial ventilatory support: a preliminary study comparing the effects of adaptive support ventilation with synchronized intermittent mandatory ventilation plus inspiratory pressure support. Crit Care Med 2002;**30**(4):801-7

18. Weiler N, Eberle B, Heinrichs W. Adaptive lung ventilation (ALV) during anesthesia for pulmonary surgery: automatic response to transitions to and from one-lung ventilation. J Clin Monit Comput 1998;**14**(4):245-52

19. Weiler N, Heinrichs W, Kessler W. The ALV-mode: a safe closed loop algorithm for ventilation during total intravenous anesthesia. International journal of clinical monitoring and computing 1994;**11**(2):85-8

20. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA : the journal of the American Medical Association 2012;**307**(23):2526-33 doi: 10.1001/jama.2012.5669[published Online First: Epub Date]|.

21. diesease GIfcol. Pocket guide to COPD diagnosis, management and prevention, 2010.

22. Hewlett AM, Platt AS, Terry VG. Mandatory minute volume. A new concept in weaning from mechanical ventilation. Anaesthesia 1977;**32**(2):163-9

23. Brunner JX, Iotti GA. Adaptive Support Ventilation (ASV). Minerva Anestesiol 2002;**68**(5):365-68

24. Campbell RS, Sinamban RP, Johannigman JA, et al. Clinical evaluation of a new closed loop ventilation mode: adaptive supportive ventilation (ASV). Critical Care 1999;**3**(Suppl 1):P038

25. Tehrani FT. Jan. 22, 1991 1991. United States patent US Patent No. 4,986,268,.

26. Tehrani FT. Automatic control of an artificial respirator. Proc IEEE EMBS Conf 1991 1993;**13**:1738-39

27. Putensen C, Hering R, Wrigge H. Controlled versus assisted mechanical ventilation. Curr Opin Crit Care 2002;**8**(1):51-7

28. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 2008;**358**(13):1327-35 doi: 10.1056/NEJMoa070447[published Online First: Epub Date]|.

29. Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 1998;**129**(6):433-40

30. Froese AB, Bryan AC. Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 1974;**41**(3):242-55

31. Putensen C, Zech S, Wrigge H, et al. Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 2001;**164**(1):43-9 doi: 10.1164/ajrccm.164.1.2001078[published Online First: Epub Date]|.

Contributorship statement

DS, GM, TB, IF, NW and CH substantially contributed to the conception and design of the study. DS drafted the first version of the manuscript. DS, GM, TB, IF, NW and CH revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

Funding

Drägerwerk AG & Co. KGAa, Lübeck, Germany provides a restricted research grant and one anesthesia machines equipped with Smart Vent Control for the conduction of the study to each of the participating study sites.

Acknowledgement

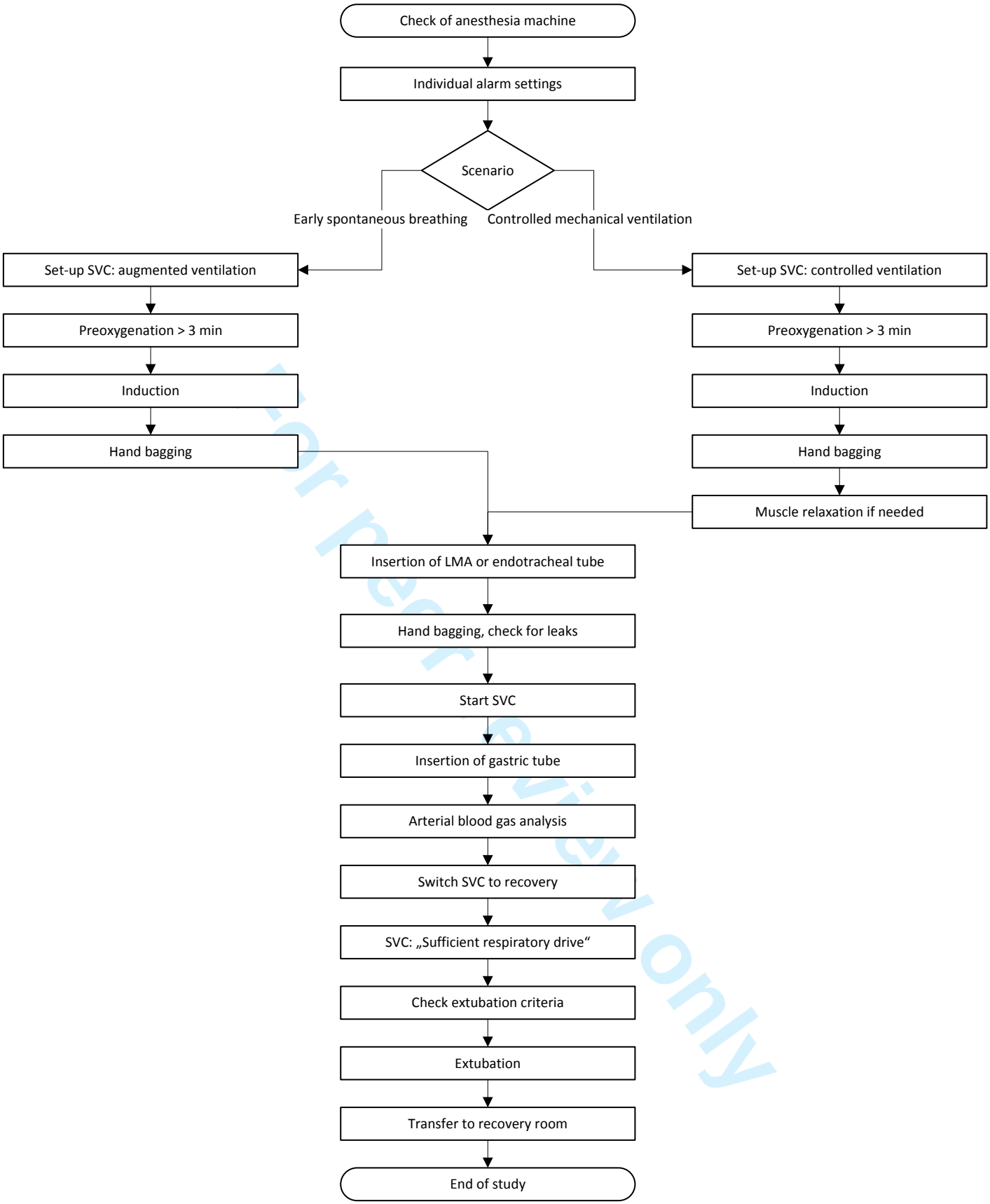
The authors would like to thank Stefan Mersmann, Drägerwerk AG & Co. KGaA, Lübeck, Germany for excellent support especially in the description of the Smart Vent Control system.

Competing interest

DS, TB, IF, NW and CH received lecture fees from Drägerwerk AG & Co. KGAa, Lübeck, Germany. DS received consultant honoraria from Drägerwerk AG & Co. KGAa, Lübeck, Germany.

Figure legend

Figure 1. Flowchart of study procedure.



AVAS trial

Automated control of mechanical **v**entilation during general **a**nae**s**thesia

A bicentric prospective observational trial

Study protocol

General information

Principle investigators

I. Prof. Dr. med. Norbert Weiler

University Medical Center Schleswig-Holstein, Campus Kiel

Department of Anesthesiology and Intensive Care Medicine

Arnold-Heller-Str. 3, Haus 12

24105 Kiel

Germany

Tel.: +49 431 597-1025

norbert.weiler@uksh.de

II. Prim. Univ.-Prof. Dr. Christoph Hörmann

State Hospital St. Pölten

Anesthesiology and Intensive Care Medicine

Propst-Führer-Straße 4

3100 St. Pölten

Austria

Tel.: +43 2742/9004-11006

Christoph.Hoermann@stpoelten.lknoe.at

Study team

I. Kiel

Prof. Dr. Norbert Weiler (principal investigator)

Dr. med. Dirk Schädler (deputy investigator)

Dr. med. Tobias Becher (investigator)

Stefanie D'aria (study nurse)

Corinna Buchholz (study nurse)

II. St. Pölten

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

Dr. med. Georg Miestinger (investigator)

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** • Planned elective surgery of the upper limb, lower limb or, peripheral vascular surgery in general anesthesia • 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 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
- 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. The responsible anesthesiologist defines a target range 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 begin of the surgical procedure an arterial blood gas analysis will be performed and the $PaCO_2$ will be measured. Then 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
Department of Anesthesiology and Intensive Care Medicine
Arnold-Heller-Str. 3, Haus 12
24105 Kiel
Germany

II. Karl Landsteiner Privat University

University Hospital St. Pölten
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:

- Planned elective surgery of the upper limb, lower limb or peripheral vascular surgery in general anesthesia
- 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
- Two or more of the following organ failures
    - Mild, moderate or severe ARDS
    - 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:
    - level of ventilation, airway and lung mechanics as clinically indicated
    - 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 (routine)
- Arterial blood gas analysis 15 minutes after the begin of the surgical procedure (routine)

- 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
- 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 (routine)
- Arterial blood gas analysis 15 minutes after the begin of the surgical procedure (routine)
- 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. Esophageal pressure swings will be recorded continuously ("fast data").

End-point determination

The end-points of the study are evaluated using the recorded data and the protocolled data of the study team.

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

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

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.
2. **Dojat M, Brochard L, Lemaire F, Harf A**: A knowledge-based system for assisted ventilation of patients in intensive care units. International journal of clinical monitoring and computing 1992;9:239-250.
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.
4. **Burns KEA, Meade MO, Lessard MR, Hand L, Zhou Q, Keenan SP, Lellouche F**: Wean Earlier and Automatically with New Technology (the WEAN Study). A Multicenter, Pilot Randomized Controlled Trial. Am J Respir Crit Care Med 2013;187:1203-1211.
5. **Lellouche F, Mancebo J, Jolliet P, Roeseler J, Schortgen F, Dojat M, Cabello B, Bouadma L, Rodriguez P, Maggiore S *et al***: A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. Am J Respir Crit Care Med 2006;174:894-900.
6. **Liu L, Xu XT, Yang Y, Huang YZ, Liu SQ, Qiu HB**: Computer-driven automated weaning reduces weaning duration in difficult-to-wean patients. Chinese medical journal 2013;126:1814-1818.
7. **Rose L, Presneill JJ, Johnston L, Cade JF**: A randomised, controlled trial of conventional versus automated weaning from mechanical ventilation using SmartCare/PS. Intensive Care Med 2008;34:1788-1795.
8. **Schädler D, Engel C, Elke G, Pulletz S, Haake N, Frerichs I, Zick G, Scholz J, Weiler N**: Automatic control of pressure support for ventilator weaning in surgical intensive care patients. Am J Respir Crit Care Med 2012;185:637-644.
9. **Stahl C, Dahmen G, Ziegler A, Muhl E**: Comparison of automated protocol-based versus non-protocol-based physician-directed weaning from mechanical ventilation. Intensivmedizin und Notfallmedizin 2009;46:441-446.
10. **Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS**: Acute respiratory distress syndrome: the Berlin Definition. Jama 2012;307:2526-2533.

Appendix

BMJ Open

Automated control of mechanical ventilation during general anesthesia – study protocol of a bicentric observational study (AVAS study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014742.R1
Article Type:	Protocol
Date Submitted by the Author:	01-Feb-2017
Complete List of Authors:	Schädler, Dirk; University Medical Center Schleswig-Holstein, Campus Kiel, Department of Anesthesiology and Intensive Care Medicine Miestinger, Georg; University Hospital St. Pölten, Department of Anesthesiology and Intensive Care Medicine Becher, Tobias; University Medical Center Schleswig-Holstein, Campus Kiel, Department of Anesthesiology and Intensive Care Medicine Frerichs, Inéz; University Medical Center Schleswig-Holstein, Campus Kiel, Department of Anesthesiology and Intensive Care Medicine Weiler, Norbert; University Medical Center Schleswig-Holstein, Campus Kiel, Department of Anesthesiology and Intensive Care Medicine Hörmann, Christoph; University Hospital St. Pölten, Department of Anesthesiology and Intensive Care Medicine
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Respiratory medicine, Surgery, Patient-centred medicine
Keywords:	Adult anaesthesia < ANAESTHETICS, Adult surgery < SURGERY, Clinical trials < THERAPEUTICS

Automated control of mechanical ventilation during general anesthesia – study protocol of a bicentric observational study (AVAS study)

Dirk Schädler[1*] MD, dirk.schaedler@uksh.de

Georg Miestinger[2] MD, georg.miestinger@stpoelten.lknoe.at

Tobias Becher[1] MD, tobias.becher@uksh.de

Inéz Frerichs[1] MD, inez.frerichs@uksh.de

Norbert Weiler[1] MD, norbert.weiler@uksh.de

Christoph Hörmann[2] MD, christoph.hoermann@stpoelten.lknoe.at

[1]Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Arnold-Heller-Straße 3, Haus 12, 24105 Kiel, Germany.
[2]Department of Anesthesiology and Intensive Care Medicine, University Hospital St. Pölten, Propst-Führer-Straße 4, St. Pölten A-3100

*Corresponding author

Abstract

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

Methods and analysis: The AVAS study is an international investigator-initiated bicentric observational study designed to examine safety and efficacy of the system during general anesthesia. 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 anesthesia without any additional regional anesthesia 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 zones 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 anesthesia machine. The study was approved by the Ethics Committee of both participating study sites. In case that

safety and efficacy are acceptable, a randomized 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

Abstract word count: 292/300

Strengths and limitations of this study

- Safety and efficacy of a novel system for the automated control of mechanical ventilation on an anesthesia machine as well as feasibility of early assisted ventilation during general anesthesia 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 randomized 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 AVAS study would be of benefit.
- The clinical value of the AVAS study will be limited due to the observational study design.

Keywords

Closed-loop-control of mechanical ventilation, knowledge based system, spontaneous breathing, general anesthesia, automatic control of artificial ventilation.

Introduction

Automated control of mechanical ventilation is a technology which has been introduced in ventilators used in the intensive care unit (ICU). Different systems (e. g. Intellivent - Adaptive Support Ventilation [1], SmartCare/PS [2], 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 for a significantly higher percentage of time than clinicians [4 5]. Several randomized 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], other studies revealed that automated systems shortened the ventilation time [12-18] when compared to weaning protocols or usual care.

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 machines. A novel system called Smart Vent Control (SVC) was designed. SVC automatically controls the mechanical breathing frequency, inspiratory time, inspiratory pressure, pressure support and trigger sensitivity and was implemented on an anesthesia 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 target zone. 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 anesthesia.

Methods and Analysis

The "**A**utomated control of mechanical **v**entilation during general **a**nesthesia **s**tudy (AVAS study) is an international investigator-initiated bicentric observational study investigating the application of SVC during general anesthesia. The study was approved by the Ethics Committee of the Medical Faculty of the Christian Albrechts University 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 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 endexpiratory pressure are not controlled automatically. SVC adjusts the ventilator settings with the aim to keep a patient stable in a target zone (TZ). Numerous predefined TZs exist that can be set according to the current therapeutic situation. All TZs can be customized by the user for each individual patient and consist of upper and lower limits for tidal volume (V_T) and for the partial pressure of end-tidal carbon dioxide ($P_{et}CO_2$). Based on these limits, the system classifies the current quality of ventilation, called Classification of Ventilation (CoV), and derives new ventilator settings accordingly. This is done every 15 seconds. 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, PCV) to assisted ventilation (pressure support ventilation, PSV) if $PetCO_2$ is classified as mild hypoventilation. The patient is continuously monitored for possible instabilities. Lastly, the physician is supported in the recovery process of general anesthesia 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 anesthesia 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 anesthesia without any additional regional anesthesia technique

- Patient is classified as American Society of Anesthesiologists (ASA) 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 (ARDS) [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
    - Hemodynamic instability defined as systolic blood pressure < 90 mm Hg, mean arterial pressure < 70 mmHg or administration of any vasoactive drugs
    - Acute renal failure defined as oliguria, i.e. 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: loss of consciousness or encephalopathy.

Study procedure

All patients will be ventilated with SVC. Since SVC does not control the inspired fraction of oxygen (F_IO_2) and positive end-expiratory pressure (PEEP), the user will have to set up both

of these settings during the whole general anesthesia with the aim to reach a peripheral saturation of oxygen (SpO_2) greater than 95%.

Anesthesia 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 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 esophageal balloon for assessment of esophageal 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 anesthesia, 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

- Check of the anesthesia 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 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 SVC
- Insertion and position check of a gastric tube (if clinically indicated)
- Arterial blood gas analysis 15 minutes after the beginning 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 SVC ventilation regime to “Recovery”

II. Controlled mechanical ventilation

- Check of the anesthesia 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 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 SVC
- 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 SVC system to "Augmented Ventilation"
- If no spontaneous breaths are detected during 20 minutes, 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 (GCS) >8, no surgical contraindication. After extubation, the patients will be monitored for at least 5 minutes 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 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 $P_{et}CO_2$ lower than 5 mm Hg of the lower target setting for SVC for longer than 5 minutes. The responsible anesthesiologist defines a target for the arterial partial pressure of carbon dioxide ($P_aCO_{2\_target}$) before the induction of the general anesthesia and sets the corresponding end-tidal 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 P_aCO_2 will be measured.
- Hypoventilation defined as $P_{et}CO_2$ higher than 5 mm Hg of the upper target setting for the SVC 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. Reasons for overriding or stopping the system will be noted.

Secondary endpoints are:

- 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) ≤ $P_aCO_2 \leq P_aCO_{2\_target} + 5$ 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 target zones 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"), 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 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.

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 5 consecutive patients.

Statistical considerations

We estimated a frequency of 3 to 5 % for the adverse events. Therefore, a sample size of n=100 patients seems reasonable. Descriptive statistical analyses (mean ± standard deviation, median and 95% confidence interval where appropriate) will be used.

Ethics and dissemination

In contrast to conventional anesthesia machines, automated control of mechanical ventilation is steadily increasing in ICU ventilators. The commercially available systems cover the control of one ventilator setting, i.e. the pressure support level during weaning (SmartCare/PS)[2]), minute ventilation (mandatory minute ventilation, MMV[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 T_I, 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 anesthesia 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 anesthesia 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 anesthesia in terms of a proof-of-concept approach. In case that safety and efficacy are acceptable (i.e. the study was not stopped per the early termination rule) in this study, a randomized controlled trial comparing SVC with the usual practice may be warranted. As spontaneous breathing may not be acceptable or possible during some surgical procedures (e. g. 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 categorize reasons for overriding 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 anesthesia conferences; second, the study will be published in a peer-reviewed journal; third, a multicenter randomized controlled study will be designed.

References

1. Arnal JM, Wysocki M, Novotni D, et al. 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**(5):781-7.

2. Dojat M, Brochard L, Lemaire F, Harf A. A knowledge-based system for assisted ventilation of patients in intensive care units. International journal of clinical monitoring and computing 1992;**9**(4):239-50.

3. Sinderby C, Navalesi P, Beck J, et al. Neural control of mechanical ventilation in respiratory failure. Nature medicine 1999;**5**(12):1433-6.

4. Dojat M, Harf A, Touchard D, Laforest M, Lemaire F, Brochard L. Evaluation of a knowledge-based system providing ventilatory management and decision for extubation. Am J Respir Crit Care Med 1996;**153**(3):997-1004.

5. Lellouche F, Bouchard PA, Simard S, L'Her E, Wysocki M. Evaluation of fully automated ventilation: a randomized controlled study in post-cardiac surgery patients. Intensive care medicine 2013;**39**(3):463-71.

6. Burns KEA, Meade MO, Lessard MR, et al. Wean Earlier and Automatically with New Technology (the WEAN Study). A Multicenter, Pilot Randomized Controlled Trial. American journal of respiratory and critical care medicine 2013;**187**(11):1203-11.

7. Dongelmans DA, Veelo DP, Bindels A, et al. Determinants of tidal volumes with adaptive support ventilation: a multicenter observational study. Anesth Analg 2008;**107**(3):932-7.

8. Petter AH, Chiolero RL, Cassina T, Chassot PG, Muller XM, Revelly JP. Automatic "respirator/weaning" with adaptive support ventilation: the effect on duration of endotracheal intubation and patient management. Anesth Analg 2003;**97**(6):1743-50.

9. Rose L, Presneill JJ, Johnston L, Cade JF. A randomised, controlled trial of conventional versus automated weaning from mechanical ventilation using SmartCare/PS. Intensive Care Med 2008;**34**(10):1788-95.

10. Schädler D, Engel C, Elke G, et al. Automatic control of pressure support for ventilator weaning in surgical intensive care patients. Am J Respir Crit Care Med 2012;**185**(6):637-44.

11. Stahl C, Dahmen G, Ziegler A, Muhl E. Comparison of automated protocol-based versus non-protocol-based physician-directed weaning from mechanical ventilation. Intensivmedizin und Notfallmedizin 2009;**46**(6):441-46.

12. Celli P, Privato E, Ianni S, et al. Adaptive support ventilation versus synchronized intermittent mandatory ventilation with pressure support in weaning patients after orthotopic liver transplantation. Transplant Proc 2014;**46**(7):2272-8.

13. Gruber PC, Gomersall CD, Leung P, et al. Randomized controlled trial comparing adaptive-support ventilation with pressure-regulated volume-controlled ventilation with automode in weaning patients after cardiac surgery. Anesthesiology 2008;**109**(1):81-7.

14. Kirakli C, Naz I, Ediboglu O, Tatar D, Budak A, Tellioglu E. A randomized controlled trial comparing the ventilation duration between adaptive support ventilation and pressure assist/control ventilation in medical patients in the ICU. Chest 2015;**147**(6):1503-9.

15. Kirakli C, Ozdemir I, Ucar ZZ, Cimen P, Kepil S, Ozkan SA. Adaptive support ventilation for faster weaning in COPD: a randomised controlled trial. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology 2011;**38**(4):774-80.

16. Lellouche F, Mancebo J, Jolliet P, et al. A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. Am J Respir Crit Care Med 2006;**174**(8):894-900.

17. Sulzer CF, Chiolero R, Chassot PG, Mueller XM, Revelly JP. Adaptive support ventilation for fast tracheal extubation after cardiac surgery: a randomized controlled study. Anesthesiology 2001;**95**(6):1339-45.

18. Zhu F, Gomersall CD, Ng SK, Underwood MJ, Lee A. A randomized controlled trial of adaptive support ventilation mode to wean patients after fast-track cardiac valvular surgery. Anesthesiology 2015;**122**(4):832-40.

19. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA : the journal of the American Medical Association 2012;**307**(23):2526-33.

20. Global Initiative for chronic obstructive lung diesease. Pocket guide to COPD diagnosis, management and prevention. Secondary Global Initiative for chronic obstructive lung diesease. Pocket guide to COPD diagnosis, management and prevention. [website] 26.10.2015 2010. http://www.goldcopd.org/uploads/users/files/GOLD_Pocket_2010Mar31.pdf.

21. Hewlett AM, Platt AS, Terry VG. Mandatory minute volume. A new concept in weaning from mechanical ventilation. Anaesthesia 1977;**32**(2):163-9.

22. Brunner JX, Iotti GA. Adaptive Support Ventilation (ASV). Minerva Anestesiol 2002;**68**(5):365-68.

23. Campbell RS, Sinamban RP, Johannigman JA, et al. Clinical evaluation of a new closed loop ventilation mode: adaptive supportive ventilation (ASV). Critical Care 1999;**3**(Suppl 1):P038.

24. Tehrani FT. Jan. 22, 1991 1991. United States patent US Patent No. 4,986,268,.

25. Tehrani FT. Automatic control of an artificial respirator. Proc IEEE EMBS Conf 1991 1993;**13**:1738-39.

26. Putensen C, Hering R, Wrigge H. Controlled versus assisted mechanical ventilation. Curr Opin Crit Care 2002;**8**(1):51-7.

27. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 2008;**358**(13):1327-35.

28. Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 1998;**129**(6):433-40.

29. Froese AB, Bryan AC. Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 1974;**41**(3):242-55.

30. Putensen C, Zech S, Wrigge H, et al. Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 2001;**164**(1):43-9.

Contributorship statement

DS, GM, TB, IF, NW and CH substantially contributed to the conception and design of the study. DS drafted the first version of the manuscript. DS, GM, TB, IF, NW and CH revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

Funding

Drägerwerk AG & Co. KGAa, Lübeck, Germany provides a restricted research grant and one anesthesia machines equipped with Smart Vent Control for the conduction of the study to each of the participating study sites.

Acknowledgement

The authors would like to thank Stefan Mersmann, Drägerwerk AG & Co. KGaA, Lübeck, Germany for excellent support especially in the description of the Smart Vent Control system.

Competing interest

DS, TB, IF, NW and CH received lecture fees from Drägerwerk AG & Co. KGAa, Lübeck, Germany. DS received consultant honoraria from Drägerwerk AG & Co. KGAa, Lübeck, Germany.

Figure legend

Figure 1. Flowchart of study procedure.

Figure 1. Flowchart of study procedure.

36x43mm (300 x 300 DPI)

AVAS trial

Automated control of mechanical **v**entilation during general **a**nae**s**thesia

A bicentric prospective observational trial

Study protocol

General information

Principle investigators

I. Prof. Dr. med. Norbert Weiler

University Medical Center Schleswig-Holstein, Campus Kiel

Department of Anesthesiology and Intensive Care Medicine

Arnold-Heller-Str. 3, Haus 12

24105 Kiel

Germany

Tel.: +49 431 597-1025

norbert.weiler@uksh.de

II. Prim. Univ.-Prof. Dr. Christoph Hörmann

State Hospital St. Pölten

Anesthesiology and Intensive Care Medicine

Propst-Führer-Straße 4

3100 St. Pölten

Austria

Tel.: +43 2742/9004-11006

Christoph.Hoermann@stpoelten.lknoe.at

Study team

I. Kiel

Prof. Dr. Norbert Weiler (principal investigator)

Dr. med. Dirk Schädler (deputy investigator)

Dr. med. Tobias Becher (investigator)

Stefanie D'aria (study nurse)

Corinna Buchholz (study nurse)

II. St. Pölten

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

Dr. med. Georg Miestinger (investigator)

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
Department of Anesthesiology and Intensive Care Medicine
Arnold-Heller-Str. 3, Haus 12
24105 Kiel
Germany

II. Karl Landsteiner Privat University

University Hospital St. Pölten
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:
    - level of ventilation, airway and lung mechanics as clinically indicated
    - 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

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.
2. **Dojat M, Brochard L, Lemaire F, Harf A**: A knowledge-based system for assisted ventilation of patients in intensive care units. International journal of clinical monitoring and computing 1992;9:239-250.
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.
4. **Burns KEA, Meade MO, Lessard MR, Hand L, Zhou Q, Keenan SP, Lellouche F**: Wean Earlier and Automatically with New Technology (the WEAN Study). A Multicenter, Pilot Randomized Controlled Trial. Am J Respir Crit Care Med 2013;187:1203-1211.
5. **Lellouche F, Mancebo J, Jolliet P, Roeseler J, Schortgen F, Dojat M, Cabello B, Bouadma L, Rodriguez P, Maggiore S *et al***: A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. Am J Respir Crit Care Med 2006;174:894-900.
6. **Liu L, Xu XT, Yang Y, Huang YZ, Liu SQ, Qiu HB**: Computer-driven automated weaning reduces weaning duration in difficult-to-wean patients. Chinese medical journal 2013;126:1814-1818.
7. **Rose L, Presneill JJ, Johnston L, Cade JF**: A randomised, controlled trial of conventional versus automated weaning from mechanical ventilation using SmartCare/PS. Intensive Care Med 2008;34:1788-1795.
8. **Schädler D, Engel C, Elke G, Pulletz S, Haake N, Frerichs I, Zick G, Scholz J, Weiler N**: Automatic control of pressure support for ventilator weaning in surgical intensive care patients. Am J Respir Crit Care Med 2012;185:637-644.
9. **Stahl C, Dahmen G, Ziegler A, Muhl E**: Comparison of automated protocol-based versus non-protocol-based physician-directed weaning from mechanical ventilation. Intensivmedizin und Notfallmedizin 2009;46:441-446.
10. **Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS**: Acute respiratory distress syndrome: the Berlin Definition. Jama 2012;307:2526-2533.

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.
2. **Dojat M, Brochard L, Lemaire F, Harf A**: A knowledge-based system for assisted ventilation of patients in intensive care units. International journal of clinical monitoring and computing 1992;9:239-250.
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.
4. **Burns KEA, Meade MO, Lessard MR, Hand L, Zhou Q, Keenan SP, Lellouche F**: Wean Earlier and Automatically with New Technology (the WEAN Study). A Multicenter, Pilot Randomized Controlled Trial. Am J Respir Crit Care Med 2013;187:1203-1211.
5. **Lellouche F, Mancebo J, Jolliet P, Roeseler J, Schortgen F, Dojat M, Cabello B, Bouadma L, Rodriguez P, Maggiore S *et al***: A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. Am J Respir Crit Care Med 2006;174:894-900.
6. **Liu L, Xu XT, Yang Y, Huang YZ, Liu SQ, Qiu HB**: Computer-driven automated weaning reduces weaning duration in difficult-to-wean patients. Chinese medical journal 2013;126:1814-1818.
7. **Rose L, Presneill JJ, Johnston L, Cade JF**: A randomised, controlled trial of conventional versus automated weaning from mechanical ventilation using SmartCare/PS. Intensive Care Med 2008;34:1788-1795.
8. **Schädler D, Engel C, Elke G, Pulletz S, Haake N, Frerichs I, Zick G, Scholz J, Weiler N**: Automatic control of pressure support for ventilator weaning in surgical intensive care patients. Am J Respir Crit Care Med 2012;185:637-644.
9. **Stahl C, Dahmen G, Ziegler A, Muhl E**: Comparison of automated protocol-based versus non-protocol-based physician-directed weaning from mechanical ventilation. Intensivmedizin und Notfallmedizin 2009;46:441-446.
10. **Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS**: Acute respiratory distress syndrome: the Berlin Definition. Jama 2012;307:2526-2533.