Avdelningen för Anestesiologi och Intensivvård, Medicinska Fakulteten
Lunds universitet

INFLUENCE OF TIDAL VOLUME ON PULMONARY GAS EXCHANGE DURING GENERAL ANAESTHESIA

Akademisk avhandling

som med vederbörligt tillstånd av Medicinska Fakulteten vid Lunds Universitet för avläggande av doktorsexamen i medicinsk vetenskap i ämnet anestesiologi och intensivvård, kommer att offentligen försvaras i föreläsningssal F3, Centralblocket, Skånes Universitetssjukhus i Lund, onsdagen den 1 juni 2011, kl. 09.15

LUND UNIVERSITY
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DOKUMENTDATABLAD enl SIS 61 41 21

Organization LUND UNIVERSITY	Document name DOCTORAL DISSERTATION
	Date of issue 1 juni 2011
	Sponsoring organization
Author(s) Bruno Enekvist	

Title and subtitle

Influence of tidal volume on pulmonary gas exchange during general anaesthesia

Abstract

Background and objective: General anaesthesia impairs respiratory function. The present studies were performed to compare arterial concentration of sevoflurane, oxygen and carbon dioxide in normal and overweight patients ventilated with increased tidal volume (VT), or normal tidal volume with and without PEEP.

Methods: Prospective, randomised, clinical studies. ASA I and II abdominal surgery patients were randomly assigned to be ventilated with normal VT (NVT) with and without PEEP to 10 cmH2O or with increased VT (IVT) achieved by increasing inspired plateau pressure 0.04 cm H2O/kg. Extra apparatus dead space was added to maintain PETCO2 at 4.5 kPa. Arterial oxygenation, sevoflurane tension (Pasevo, Fisevo, PETsevo), PaCO2, PETCO2, stroke volume, cardiac output, VT and airway pressure were measured.

Results: The groups of patients compared were similar regarding gender, age, and BMI. Arterial oxygen and sevoflurane tension was generally higher in the IVT group ($P < 0.05$) whereas mean FiO2 and PETsevo did not differ between the groups. Arterial carbon dioxide was significantly lower with IVT than NVT ventilated without PEEP but in the presence of PEEP in the NVT group, the groups were similar. Cardiac output decreased significantly less in the IVT group compared to the NVT group with PEEP (5 and 33 % respectively).

Conclusion: Isocapnic ventilation with larger tidal volumes maintained with added apparatus dead-space increases the arterial oxygen and sevoflurane tension as well as carbon dioxide elimination in normal and overweight patients, and in overweight patient also preserves cardiac output better than in the presence of PEEP.

Key words: anaesthesia, sevoflurane, cardiac output, functional residual capacity, pulmonary gas exchange

Classification system and/or index termes (if any):

Supplementary bibliographical information:		Language Englich
ISSN and key title:		ISBN 978-91-86871-04-8
Recipient's notes	Number of pages	Price
	Security classification	

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Lund University, Faculty of Medicine, Doctoral Dissertation Series 2011: 55

ISBN 978-91-86871-04-8
ISSN 1652-8220
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Lund University, Faculty of Medicine
Doctoral Dissertation Series 2011: 55

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Methods: Prospective, randomised, clinical studies. ASA I and II abdominal surgery patients were randomly assigned to be ventilated with normal V_T (NV_T) with and without PEEP to 10 cmH_2O or with increased V_T (IV_T) achieved by increasing inspired plateau pressure 0.04 cm H_2O kg^{-1}. Extra apparatus dead space was added to maintain $P_{ET}CO_2$ at 4.5 kPa. Arterial oxygenation, sevoflurane tension ($P_a$sevo, $F_i$sevo, P_{ET}sevo), P_aCO_2, $P_{ET}CO_2$, stroke volume, cardiac output, V_T and airway pressure were measured.

Results: The groups of patients compared were similar regarding gender, age, and BMI. Arterial oxygen and sevoflurane tension was generally higher in the IV_T group ($P < 0.05$) whereas mean F_iO_2 and P_{ET}sevo did not differ between the groups. Arterial carbon dioxide was significantly lower with IV_T than NV_T ventilated without PEEP but in the presence of PEEP in the NVT group, the groups were similar. Cardiac output decreased significantly less in the IV_T group compared to the NV_T group with PEEP (5 and 33 % respectively).

Conclusion: Isocapnic ventilation with larger tidal volumes maintained with added apparatus dead-space increases the arterial oxygen and sevoflurane tension as well as carbon dioxide elimination in normal and overweight patients, and in overweight patient also preserves cardiac output better than in the presence of PEEP.

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List of publications

The present thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I. Enekvist B., Luttropp H.H. & Johansson A. The effect of increased apparatus dead-space and tidal volumes on carbon dioxide elimination and oxygen saturations in a low-flow anaesthesia system. *J Clin Anesth* 2008; **20**,170-4.

II. Enekvist B., Bodelsson M., Sturesson L. & Johansson A. Larger tidal volume increases sevoflurane uptake in blood – a randomized clinical study. *Acta Anaesthiol Scand*. 2010; **54**, 1111-6.

III. Enekvist B., Bodelsson M. & Johansson A. Increased apparatus dead-space and tidal volume enhances uptake of oxygen and sevoflurane in overweight patients – a randomized clinical study. *Eur J Anaesthesiol* 2011; In press.

IV. Enekvist B., Bodelsson M., Chew M. & Johansson A. Increased tidal volume during anaesthesia is superior to PEEP: impact on arterial concentration of sevoflurane, oxygenation and cardiac output in a randomised clinical study of overweight patients. Manuscript.

Abbreviations

ANOVA	Analysis of variance
ASA	Physical status according to the classification of American society of Anesthesiologists
BMI	Body mass index
CO	Cardiac output
DS	Dead-space
DS-group	Dead-space group = (Paper I) IV_T group
ECHO	Echocardiogram
ERV	Expiratorisk reserv-volym (In Swedish summary)
FGF	Fresh gas flow
F_iCO_2	Inspiratory fraction of carbon dioxide
FID	Flame ionization detector
F_iO_2	Inspiratory fraction of oxygen
$F_i$sevo	Inspiratory fraction of sevoflurane
FRC	Functional residual capacity
GC	Gas chromatography
HME	Heat and moisture filter
I/E	Inspiratory/expiratory ratio
IPPV	Intermittent positive pressure ventilation
IV_T	Increased tidal volume
MAP	Mean arterial blood pressure
NDS	Non dead-space
NDS-group	Non dead-space group = (Paper I) NV_T group
NV_T	Normal tidal volume

P_aO_2	Arterial oxygen tension
P_aCO_2	Arterial carbon dioxide tension
$P_a$sevo	Arterial sevoflurane tension
$P_{ET}CO_2$	End-tidal carbon dioxide partial pressure
P_{ET}sevo	End-tidal partial pressure of sevoflurane
PEEP	Positive end-expiratory pressure
S_aO_2	Arterial Oxygen saturation
S_PO_2	Oxygen saturation, as measured by pulse oximeter
SV	Stroke volume
TEE	Transoesophageal echocardiography
V_A	Alveolar ventilation
V_T	Tidal volume
V/Q	ventilation perfusion ratio
ZEEP	Zero end-expiratory pressure

Background

Airway collapse

Respiratory function and pulmonary gas exchange are regularly impaired during general anaesthesia. The volume of gas inspired in a normal breath is called tidal volume (V_T). The volumes of gas remaining in the lungs after a maximal expiration are called residual volume. The volume of gas remaining in the lung after a normal expiration is the functional residual capacity (FRC). Gas transport between the atmosphere and the blood is determined by the size of FRC, which is also an important component of pulmonary oxygen reserve.[1] Reduced FRC parallels a reduced residual volume, making airway closure more frequent. Several authors describe a relationship between airway closure and the body constitution under general anaesthesia with mechanical ventilation, that is the FRC and lung compliance decreases exponentially in the supine position with increased body mass index (BMI).[2, 3] Factors negatively affecting FRC is the change from seated to supine position, which normally reduces it with 0.8-1.0 L.[4] With induction of anaesthesia FRC is further reduced with another 0.4-0.5 L by reduced chest muscle tone and cranial displacement of diaphagram caused by the anaesthetic drugs.[4, 5]

Airway closure is a likely explanation for the appearance of regions with low ventilation to perfusion ratio from atelectasis during anaesthesia.[1, 2] Atelectasis appears in around 90% of all patients after induction of anaesthesia.[6-8] In addition, morbid obesity during general anaesthesia and paralysis lead to even more atelectasis and an increased risk of hypoxemia.[3] Hedenstierna and colleagues found that airway closure affects ventilation perfusion ratios (V/Q ratio) which can be prevented by increasing FRC using a positive end expiratory pressure (PEEP).[1] Adding PEEP, increases FRC and thereby prevents alveolar collapse. However, by increasing intrathoracic pressure, PEEP can also decrease the venous return to the heart, and this decrease can lead to an impaired stroke volume and cardiac output in normo- and hypovolemic patients.[9-12]

The rate of uptake of volatile anaesthetics from alveoli to the blood is dependent on the alveolar concentration and the blood solubility of the anaesthetic, as well as cardiac output. Initial alveolar concentration is enhanced by a larger FRC,

increased alveolar ventilation (V_A) and increased inspiratory gas concentration.[13, 14]

Since general anaesthesia in obese patients can lead to an increased incidence of airway collapse and subsequent problems with oxygenation an alternative to PEEP, with its negative effects on airway pressure and cardiac output would be welcome. This may be a ventilations technique with larger tidal volume.

Anaesthesia ventilators

Anaesthesia systems used in Swedish health care today usually consist of a partial rebreathing system with a carbon dioxide absorber and a monitoring system that allows an anesthesia low-flow technique. Patients are normally ventilated with intermittent positive pressure ventilation (IPPV), the initial inspiratory phase generated when the ventilator opens an inspiratory valve. This phase is active and a positive pressure builds in the patient's thorax.

During the period between closure of the inspiratory valve closes to the expiratory valve opens, gases are not able to leave the lungs througt the airways and the positive intrathoracic pressure drops to the plateau pressure ($P_{plateau}$). The rationale for the period when the $P_{plateau}$ occurs is to balance the effects of variations in pulmonary time constants between different lung compartments in order to ensure homogeneity of gas distribution. The net effect is an improved matching of ventilation and perfusion.[15] The expiratory phase begins when the expiratory valve opens, and the airway pressure then drops to atmospheric pressure or to a previously set PEEP. The expiratory phase is passive and depends on the chest and diaphragmatic recoil, which allows the patient to exhale.[16]

Since the first step of anaesthetic uptake is dependent on ventilator settings e.g. frequency, V_T and inspiratory/expiratory (I/E) ratios, different ventilation modes, should probably also affect oxygenation and/or elimination of carbon dioxide.[17] At an identical setup of fresh gas flow, frequency and I/E ratio, variations in apparatus dead-space and V_T should probably affect ventilation/perfusion ratios.

Tidal volume

Several classical textbooks of anaesthesiology describe volume-controlled ventilation with a technique using a ventilation frequency of 8-16 breaths per minute and V_T of 10-12 ml kg^{-1} body weight to avoid airway collapse/airway closures.[16, 18] These traditionally larger V_T have in the recent decennium, however, decreased to VT of around 6 ml kg^{-1} estimated ideal weight predicted according to Lemmen.[19] PEEP is commonly used for lung protective ventilation in intensive

care patients. The reason for this is to avoid increased airway pressures and/or stretching of lung tissues and thus to reduce the risk of baro-/volotrauma.[20-22] This protective ventilation has also been adopted in anaesthesia departments for ventilation in anesthetized patients during surgery. Luttropp and Johansson observed as an incidental finding in a study exploring low-flow technique with larger apparatus dead-space volumes, that the arterial oxygen tension of the patients increased (unpublished data).[23] Taken together, it is possible that larger V_T, perhaps together with larger apparatus dead-space, can affect the patient's oxygenation and perhaps also carbon dioxide elimination as well as uptake of anaesthetics during general anaesthesia.

PEEP

As already discussed, the most common technique to prevent atelectasis formation is to use PEEP. PEEP increases FRC and thereby prevents airway closure and lung collapse in the expiratory phase. However, PEEP also increases intrathoracic pressure that impairs the venous return to the heart, which normally reduces stroke volume and cardiac output.[9-12]

There is a relationship between airway closure and perfusion of poorly ventilated lung regions.[24] Hedenstierna and colleagues concluded that airway closure and thereby the ventilation to perfusion mismatch can be prevented by increasing FRC with PEEP.[13] Futier and colleagues, however, recently showed that although PEEP improves the end-expiratory lung volume, P_aO_2 after the anaesthesia induction remains unchanged.[25] The reasons for these conflicting results are not clear.

The application of PEEP is nowadays routine during general anaesthesia, and a PEEP of 10 cmH_2O has been presented as the best compromise between highest compliance and lowest dead space fraction.[26-28] There may, however, be a possibility that larger V_T have a similar positive effect on the FRC and prevention of lung collapse.

Aims of the studies

The present studies were undertaken in order to investigate.

1. If a larger tidal volume, with an unchanged $P_{ET}CO_2$ and F_iO_2 affects carbon dioxide elimination, arterial blood oxygenation and/or arterial concentration of volatile anaesthetics in normal or overweight patients.
2. If a larger tidal volumes affects carbon dioxide elimination, arterial concentration of sevoflurane and oxygen and/or cardiac output similarly to normal tidal volumes with added 10 cmH_2O PEEP in overweight patients.

Materials and methods

Patients

The studies were approved by the Regional Ethics Committee (Lund, Sweden) according to the standards set in the Helsinki declaration. In all studies consent to participate were received from each patient. Patients with known pulmonary or cardiovascular disease were excluded. The investigations included ASA physical status 1 or 2 patients, scheduled for abdominal surgery. Patients were considered for inclusion in the trial if they were over 18 yr age. All procedures were estimated to last more than 60 minutes (120 min in study I). The patients in study I were included regardless of BMI, while the patients in study II all had a BMI less than 25 and the patients in study III and IV all had a BMI more than 25. The number of patients in each study is found in Table 1. Patients were randomized to one of two equally sized groups via randomly mixed sealed envelope assignment at the start of the procedure in the operating theatre.

Table 1 Patient data.

Groups	Number of patients (n)	Female /Male (n)	Age (years)	Weight (kg)	Height (meter)	BMI (kg m^{-2})
Study I						
NV_T	29	6/23	64 [58-69]	81 [75-95]	1.75 [1.67-1.80]	28 [24-30]
IV_T	30	9/21	62 [54-69]	75 [67-89]	1.75 [1.69-1.79]	26 [24-28]
Study II						
NV_T	10	5/5	70 [61-83]	63 [58-71]	1.70 [1.67-1.76]	23 [19-24]
IV_T	10	6/4	66 [42-72]	63 [47-75]	1.69 [1.54-1.79]	22 [19-24]
Study III						
NV_T	10	6/4	64 [52-78]	84 [78-101]	1.64 [1.60-1.75]	30 [26-36]
IV_T	10	5/5	64 [54-68]	81 [79-85]	1.74 [1.65-1.77]	27 [26-28]
Study IV						
NV_T	15	4/11	65 [60-72]	82 [75-89]	1.76 [1.65-1.80]	27 [25-28]
IV_T	15	4/11	58 [47-74]	90 [85-95]*	1.79 [1.68-1.84]	27 [26-31]

Values are median with interquartile range within brackets. The two groups in each study were similar and there was no difference between the groups regarding gender, age, weight, length or Body Mass Index (BMI) except the median weight of the patients in the IVT group (study IV) was somewhat larger. Mann-Whitney test, (*, $P < 0.05$).

Experimental procedure

Anaesthesia procedure

In the studies, anaesthesia was induced with 2 µg kg^{-1} fentanyl and 1.5-3 mg kg^{-1} propofol. Rocuronium (study I and IV) or atracurium (study II and III) 0.6 mg kg^{-1}, was administered for muscle paralysis. Ventilation was assisted manually with 100% oxygen via a semi open circle system (4.5 L volume) until tracheal intubation and then by means of ventilator with an F_iO_2 at 0.35 in nitrogen. The respiratory rate was set to 15 min^{-1} and V_T was adjusted as to achieve a $P_{ET}CO_2$ at 4.5 kPa. No positive end expiratory pressure (PEEP) was applied. In study I the arterial cannula was inserted in the radial artery between the tracheal intubation and sevoflurane administration. In studies II-IV propofol 8 mg kg^{-1} h^{-1} was infused until an arterial cannula had been inserted in the radial artery. A control (time Zero) sample of arterial blood was obtained.

In all studies extra doses of fentanyl (50-100 µg) were given if mean arterial blood pressure (MAP) increased more than 20% above the initial baseline level. Hypotension (MAP less than 60 mmHg) was treated with 5-10 mg ephedrine intravenously in study I-III and treated with 5-10 µg norepinephrine intravenously in study IV. All patients received 3-5 ml kg^{-1} h^{-1} of glucose solution 2.5% with sodium (70 mmol l^{-1}), chloride (45 mmol l^{-1}) and acetate (25 mmol l^{-1}) intravenously. Neuromuscular blockade was monitored with a neuromuscular transmission analyzer (TOF-Watch™; Organon Technology B V., Boxel Netherlands).

Monitoring

Patients were monitored and the following data was collected (In studies I-III: Intelli Vue MP70 Anaesthesia, Philips Medizin System, Boeblingen Germany and in study IV: Solar 8000, General Electric Medical System, Milwaukee, WI, USA), three-lead ECG, heart rate, oxygen saturation (as measured by pulse oximeter, S_pO_2) and invasive arterial blood pressure via the arterial cannula. Inspiratory and expiratory oxygen partial pressure (F_iO_2, $P_{ET}O_2$), carbon dioxide inspiratory and expiratory partial pressure (F_iCO_2, $P_{ET}CO_2$) and in studies II-IV sevoflurane inspiratory and expiratory partial pressure ($F_i$sevo, P_{ET}sevo) was analyzed by the ventilator (Dräger Primus™, Dräger Medical, Lübeck, Germany). Total ventilation per minute, V_T and airway pressures as peak pressure, plateau pressure and mean pressure were measured and documented after the start of the sevoflurane administration. Static compliance of the respiratory system was calculated as tidal volume divided by the inspiratory plateau pressure.

In study IV, stroke volume (SV) and cardiac output (CO) was assessed in 20 patients (10 in each group) with LIDCO Rapid® (LiDCO Ltd, Cambridge, UK). Trans oesophageal echocardiography (TEE) was used to assess cardiac output at

the start of anaesthesia in 6 patients (3 in each group) with Philips CX-50®, TEE ultrasound X7-2t (Philips Ultrasound, Bothell, WA, USA).

Figure 1 Ventilation with larger V_T with isocapnia accomplished with an increased apparatus dead space. The $P_{ET}CO_2$ was adjusted to 4.5 kPa with a flexible corrugated hose inserted between the Y-piece of the anaesthesia circle system and the heat and moisture filter attached to the endotracheal tube.

Ventilation techniques

In all studies, before start of anaesthesia, an unused carbon dioxide absorber was applied (Drägersorb, Dräger Medical, Lübeck, Germany) to the anaesthesia ventilator. All patients were preoxygenated with 100% oxygen for 3-4 minutes and a fresh gas flow (FGF) of 5 L^{-1}.

Respiratory rate was set to 15 min^{-1}. In the normal tidal volume groups (NV_T) V_T was adjusted to achieve a $P_{ET}CO_2$ at 4.5 kPa. PEEP 10 cmH_2O was only applied in study IV. In the increased tidal volume groups (IV_T) initial plateau pressure ($P_{plateau}$) was monitored and then V_T was increased until $P_{plateau}$ was 0.04 cmH_2O kg^{-1} over the initial $P_{plateau}$. $P_{ET}CO_2$ was then adjusted to 4.5 kPa with a flexible corrugated hose (disposable plastic tube, Medcore, AB Uppsala, Sweden) placed between the Y-piece of the anaesthesia circle system and the heat and moisture filter (HME) attached to the endotracheal tube (Fig. 1).[23] This flexible corrugated hose increased the dead-space volume and thus provided adjustable rebreathing of carbon dioxide. In both groups, inspiratory:expiratory ratio was 1:2 including an inspiratory plateau of 10 %. When stable $P_{ET}CO_2$ values reached 4.5 kPa, a control sample of arterial blood was obtained and sevoflurane administration was

started with a vaporizer (sevoflurane Dräger Vapor 2000: Medical, Lübeck, Germany) adjusted to an end-tidal concentration of 1.3% in study I. In study II-IV the vaporizer was set to 3%. After 5 minutes, the FGF was adjusted to 1.0 L min^{-1} with an unchanged vaporizer setting throughout the anaesthesia period. A schematic flow chart of the ventilatory patterns and measurements is shown in Figure 2.

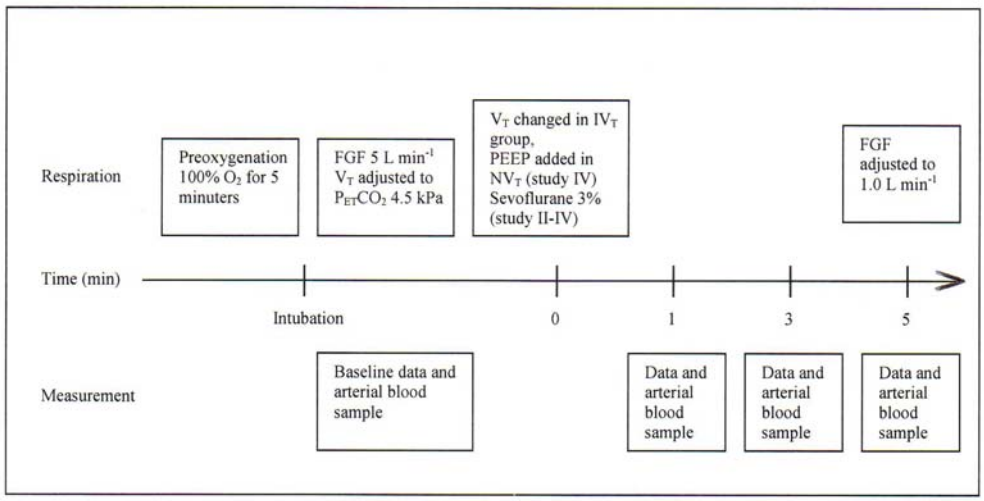

Figure 2 Schematic overview of ventilatory pattern and measurements during preparation and the first five minutes of the study.

Analysing procedure

In study I blood samples of 1.5 ml were drawn from the arterial line into heparinized syringes at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes after the start of ventilation (totally 17 ml).In study II-IV blood samples of 3 ml were drawn from the arterial line into heparinized syringes at 1, 3, 5, 10, 15, 30, 45 and 60 minutes after the start of the sevoflurane administration (totally 27 ml). Arterial oxygen tension (P_aO_2), oxygen saturation (S_aO_2) and carbon dioxide tension (P_aCO_2) was analyzed using an automatic blood gas analyzer (ABL 725™, Radiometer, Copenhagen Denmark).

Gas chromatography

In study II-IV arterial sevoflurane tension was analyzed with gas chromatography (GC) on a Perkin-Elmer 3920 gas liquid chromatograph (Perkin-Elmer 3920 gas liquid chromatograph, CT, USA).The concentration of a particular gas in a sample can be analysed using a gas chromatograph (GC) equipped with a flame ionization detector (FID). Gas chromatography is also suitable for liquid substances that easily evaporate e.g. by heat. The sample is injected with a syringe in the injector where the sample is vaporized and carried by a carrier gas, usually helium or nitrogen, through the column. Different columns are filled with fine grained material with different properties and components of the gas are separated. E.g. components that boil at low temperatures could transport easier with the carrier gas and will be detected before other components that have a higher boiling point. Other columns, as the one used in the present study, retain components based on their lipid solubility. Benefits of GC are that analysis of volatile organic compounds can be performed efficiently and that the method allows quantitative analysis of very small sample sizes. Measuring sevoflurane in blood using GC can therefore be a way to analyse if different V_T affect uptake during anaesthesia. For details on the protocol used please se refs Walther-Sturesson and Smith, Sapsed-Byrne.[29, 30]

LiDCO

The LiDCO system is a cardiac output monitoring apparatus that uses waveform pulse contour analysis via an arterial catheter. The device uses a proprietary algorithm to analyze the pulse contour by using patient specific data from a patient monitor.[31] Linton and colleagues found a good conformity between thermo dilutions and LiDCO measurements in 40 patients, with a linear regression value

of 0.94.[32] Calculation of SV and CO with LiDCO via the arterial cannula, is an easy and safe method, and might detect if the size of the V_T has hemodynamic effects compared with PEEP.

Transoesophageal echocardiography

An echocardiogram, (cardiac ECHO), is a sonogram of the heart. Also known as a cardiac ultrasound, it uses standard ultrasound techniques to image two-dimensional slices of the heart. The latest ultrasound systems also employ 3D real-time imaging and can be recorded. In addition to creating two-dimensional pictures of the cardiovascular system, an ECHO can also produce accurate assessment of the velocity of blood and visualisation of different cardiac tissue at any arbitrary point using pulsed or continuous wave Doppler ultrasound. It also allows assessment of cardiac valve areas and function, any abnormal communications between different sides of the heart and calculation of the cardiac output as well as the ejection fraction. A specialized probe containing an ultrasound transducer at its tip can be managed into the patient's oesophagus/ventricle, a technique known as a transoesophageal echocardiogram (TEE). TEE can quickly assess the patient's heart valves and degree of heart muscle contraction. The use of TEE for measuring cardiac output could therefore be a way of validating the outcome of a LiDCO measurement.

Statistics

For details on the statistic methods used the reader is referred to the respective studies I-IV.
In brief, data analyses were as follows:

- In all studies an initial power analysis was performed to estimate the number of observations needed to achieve a power over 0.8 at $P < 0.05$.
- All statistical analysis was performed with SPSS for Windows (SPSS Inc., Chicago, Illinois, USA).
- For examination of normally distributed continuous data, as determined using analysis with a Gaussian distribution test, data is presented as mean values and variability quantified with SD. Data was analyzed with a two-tailed t-test.
- During examination of not normally distributed continuous or categorical data, data is presented as median and variability quantified with inter quartile range. Data was analyzed with a non-parametric method (Mann-Whitney-U test).

- For change of values over time, two-way analysis of variance (ANOVA) for repeated measurements was used. The ANOVA was followed by Greenhouse-Geisser post hoc test to avoid multiple significances.
- A P-value < 0.05 was considered to indicate statistical significance.

Results

For demographic data please see Table 1. No intraoperative problems were noted during the studies. All patients recovered from anaesthesia and left the postoperative unit in accordance with the routines assigned for the various surgical procedures.

Table 2 Comparison of the values for expiratory carbon dioxide ($P_{ET}CO_2$), carbon dioxide tension in arterial blood (P_aCO_2), P_aCO_2-$P_{ET}CO_2$ difference (P_a-$P_{ET}CO_2$) and lung compliance after 60 minutes between normal tidal volume group (NV_T) and increased tidal volume group (IV_T).

Groups	**$P_{ET}CO_2$ (kPa)**	**P_aCO_2 (kPa)**	**P_a-$P_{ET}CO_2$ (kPa)**	**Lung Compliance (ml cmH_2O^{-1})**
Study I				
NV_T	4.5 ± 0.1	5.1 ± 0.24	0.63 ± 0.3	31 [28-39]
IV_T	4.6 ± 0.2	4.8 ± 0.25*	0.31 ± 0.2*	42 [37-50]*
Study II				
NV_T	4.5 ± 0.07	5.7 ± 0.37	1.09 ± 0.35	31 [28-34]
IV_T	4.5 ± 0.13	4.9 ± 0.27*	0.42 ± 0.26*	44 [33-48]*
Study III				
NV_T	4.4 ± 0.22	5.5 ± 0.31	1.1 ± 0.30	27 [21-31]
IV_T	4.5 ± 0.07	5.0 ± 0.20*	0.53 ± 0.21*	41 [31-52]*
Study IV				
NV_T	4.5 ± 0.08	5.6 ± 0.50	1.1 ± 0.51	39 [34-43]
IV_T	4.5 ± 0.07	5.2 ± 0.56	0,7 ± 0.51*	40 [36-49]

Values are mean ± SD, except lung compliance value which are median [inter quartile range]. For "n" please see Table 1. $P_{ET}CO_2$ values were similar between the two groups (paper I-IV). * denotes statistically significant difference between groups. Independent two-tailed t-test and Two-Way repeated measurement ANOVA followed by Greenhouse-Geisser post hoc test, Mann-Whitney U test, respectively, ($P < 0.05$).

Carbon dioxide

In all studies mean $P_{ET}CO_2$ were similar between the two groups (Table 2). Mean P_aCO_2 was statistically significantly lower in the IV_T group throughout the observation period ($P < 0.05$, Table 2) except in study IV where the difference did

not reach statistical significance. The difference between P_aCO_2 and $P_{ET}CO_2$ was, however, statistically significantly smaller in the IV_T group compared to the NV_T group in all studies ($P < 0.05$, Table 2).

Table 3 Comparison of the values for the inspiratory oxygen concentrations (F_iO_2), oxygen saturation in arterial blood, (S_aO_2), oxygen tension (P_aO_2), between normal tidal volume group (NV_T) and increased tidal volume group (IV_T).

	Groups	5 min	30 min	60 min
Study I				
F_iO_2 (%)	NV_T	38 ± 4.8	36 ± 2.2	35 ± 0.9
	IV_T	37 ± 3.3	35 ± 2.0	35 ± 1.7
S_aO_2 (%)	NV_T	99 [97-100]	99 [96-100]	100 [99-100]
	IV_T	99 [99-100]	99 [98-100]	100 [99-100]
P_aO_2 (kPa)	NV_T	16 ± 4.6	15 ± 4.3	15 ± 4.8
	IV_T	18 ± 4.0	17 ± 4.9	16 ± 4.0
Study II				
FiO_2 (%)	NV_T	34 ± 1.9	35 ± 0.79	36 ± 1.3
	IV_T	35 ± 0.6	34 ± 0.82	35 ± 0.7
S_aO_2 (%)	NV_T	99 [96-99]	99 [96-99]	99 [97-100]
	IV_T	99 [99-100]*	99 [99-100]*	100 [99-100]*
P_aO_2 (kPa)	NV_T	18 ± 5.1	17 ± 5.1	15 ± 4.3
	IV_T	21 ± 3.2*	20 ± 4.0*	21 ± 4.9*
Study III				
F_iO_2 (%)	NV_T	35 ± 2.1	37 ± 2.34	37 ± 5.5
	IV_T	35 ± 1.0	35 ± 0.96	35 ± 0.5
S_aO_2 (%)	NV_T	96 [92-98]	96 [92-98]	94 [91-98]
	IV_T	100 [99-100]*	99 [98-99]*	99 [98-100]*
P_aO_2 (kPa)	NV_T	11 ± 3.8	11 ± 2.9	10 ± 2.7
	IV_T	16 ± 3.0*	17 ± 3.8*	15± 4.3*
Study IV				
F_iO_2 (%)	NV_T	35 ± 0.83	35 ± 0.83	35 ± 0.70
	IV_T	35 ± 1.0	35 ± 0.83	35 ± 0.46
S_aO_2 (%)	NV_T	98 [97-98]	98 [97-99]	98 [97-99]
	IV_T	98 [97-99]*	99 [98-99]*	99 [98-99]*
P_aO_2 (kPa)	NV_T	14 ± 2.3	16 ± 2.2	15 ± 2.8
	IV_T	16 ± 3.4*	19 ± 3.6*	19 ± 3.3*

Values of S_aO_2 are median [inter quartile range] and values of F_iO_2 and P_aO_2 are mean ± SD, for "n" please see Table 1. * denotes statistically significant difference between groups, Mann-Whitney test and Two-Way repeated measurement ANOVA followed by Greenhouse-Geisser post hoc test, respectively, ($P < 0.05$).

Concentrations of sevoflurane

Levels of sevoflurane were measured in study II-III. $F_i$sevo was not statistically different between the groups (Table 4).Mean $P_a$sevo was larger in the IV_T group compared to the NV_T group over the entire measurement period and the difference tended to increase with time ($P < 0.05$, Table 4). Mean P_{ET}sevo did not differ between the groups except for after one and three minutes when P_{ET}sevo was higher in the NV_T group. The difference between $P_a$sevo and P_{ET}sevo was therefore smaller in the IV_T group compared to the NV_T group ($P < 0.05$, values not shown).

Table 4 Comparison of the values for the expiratory sevoflurane concentrations (P_{ET}sevo) and arterial sevoflurane tensions ($P_a$sevo) between normal tidal volume group (NV_T) and increased tidal volume group (IV_T).

	Groups	5 min	15 min	30 min	60 min
Study II					
P_{ET}sevo (kPa)	NV_T	2.1 ± 0.25	1.8 ± 0.18	1.9 ± 0.20	1.9 ± 0.23
P_{ET}sevo (kPa)	IV_T	2.0 ± 0.16	1.9 ± 0.13	2.0 ± 0.13	2.1 ± 0.21
$P_a$sevo (kPa)	NV_T	1.5 ± 0.37	1.5 ± 0.22	1.6 ± 0.23	1.6 ± 0.25
$P_a$sevo (kPa)	IV_T	1.7 ± 0.13*	1.7 ± 0.15*	1.8 ± 0.16*	1.9 ± 0.23*
Study III					
P_{ET}sevo (kPa)	NV_T	2.1 ± 0.15	1.8 ± 0.17	1.8 ± 0.18	1.9 ± 0.22
P_{ET}sevo (kPa)	IV_T	1.9 ± 0.15	1.7 ± 0.24	1.8 ± 0.21	1.9 ± 0.19
$P_a$sevo (kPa)	NV_T	1.4 ± 0.22	1.3 ± 0.22	1.4 ± 0.21	1.4 ± 0.19
$P_a$sevo (kPa)	IV_T	1.6 ± 0.17*	1.6 ± 0.29*	1.7 ± 0.19*	1.7 ± 0.18*
Study IV					
P_{ET}sevo (kPa)	NV_T	2.0 ± 0.18	1.6 ± 0.18	1.8 ± 0.21	1.8 ± 0.23
P_{ET}sevo (kPa)	IV_T	1.8 ± 0.21	1.8 ± 0.24	1.8 ± 0.17	1.9 ± 0.22
$P_a$sevo (kPa)	NV_T	1.2 ± 0.22	1.2 ± 0.23	1.3 ± 0.19	1.4 ± 0.21
$P_a$sevo (kPa)	IV_T	1.4 ± 0.25*	1.6 ± 0.24*	1.7 ± 0.20*	1.7 ± 0.19*

Values are mean ± SD, for "n" please see Table 1 P_{ET}sevo values were not significantly different between the groups after 5 min. Arterial sevoflurane tensions were statistically significantly higher in the IV_T group compared to the NV_T group. Two-Way repeated measurement ANOVA followed by Greenhouse-Geisser post hoc test (*, $P < 0.05$).

Tidal volumes, airway and compliance

In all studies V_T were significantly larger in the IV_T group compared to the NV_T group (Table 5). In study I-III median airway pressure was higher in the IV_T group compared to the NV_T group although the difference in plateau pressure did

not reach statistical significance. In study IV the plateau and mean airway pressure was lower in the IV_T group compared to the NV_T group with added PEEP please see (Table 5). Mean airway pressure was not registered in study I.

Table 5 Comparison of tidal volumes (V_T), tidal volume kg body weight^{-1} (total weight), peak, plateau and mean airway pressures in the normal tidal volume group (NV_T) and increased tidal volume group (IV_T) value after 60 minutes' study.

Groups	V_T (ml)	V_T (ml kg^{-1})	P-Peak (cmH_2O)	P-Plateau (cmH_2O)	P-Mean (cmH_2O)
Study I					
NV_T	452 [419-521]	5.7 [5.2-6.1]	20 [15-22]	15 [12-17]	-
IV_T	762 [758-828]*	10 [8.2-11]*	28 [24-31]*	17 [15-19]	-
Study II					
NV_T	350 [328-393]	5.7 [5.1-6.4]	14 [12-15]	12 [11-12]	4.0 [3.8-4.3]
IV_T	700 [550-750]*	11 [9.4-13]*	21 [19-23]*	16 [15-17]*	6.0 [5.8-7.0]*
Study III					
NV_T	397 [362-428]	5.0 [4.5-5.1]	16 [14-23]	15 [13-20]	4,0 [4.0-6.3]
IV_T	717 [692-807]*	9.0 [8.7-9.8]*	25 [23-26]*	18 [15-22]	7.0 [6.8-9.0]*
Study IV					
NV_T	433 [413-467]	5.2 [5.1-5.7]	22 [21-24]	21 [20-22]	13 [13-14]
IV_T	733 [680-820]*	8.6 [8.1-8.8]*	24 [21-27]	17 [15-20]*	7.0 [6.0-7.0]*

Values are median [inter quartile range]. For "n" please see Table 1. * denotes statistically significant difference between groups, Mann-Whitney U test, ($P < 0.05$).

In study I – IV the mean adjustable dead-space volume between the Y-piece and HME was between 2.8 - 3.4 ml^{-1} kg in the IV_T group.

In study I - III the lung compliance were higher in the IV_T group throughout the observation period. In study IV (PEEP of 10 cmH_2O added to the NV_T group), lung compliance was similar in the two groups throughout the observation period (Table 2).

Stroke volumes and cardiac output

In study IV baseline stroke volumes and cardiac output calculated via LiDCO measurement were similar in the two groups, but after five minutes there was a significantly lower value in the NV_T group compared to the IV_T group ($P < 0.05$, Table 6). Cardiac output decreased significantly less in the IV_T group compared to the NV_T group, (5 and 33 %, respectively, $P < 0.05$, Table 6). There was a correlation between cardiac output differences and mean airway pressure between the two groups but not within each group ($r^2 = 0.55$, Fig 3, $P < 0.05$). TEE was

performed on six patients (three in each group), and demonstrated that stroke volume was unaffected in the IV_T group and decreased 12 % in the NV_T group.

Table 6 Comparison of the values for stroke volume (SV) and cardiac output (CO) between normal tidal volume group (NV_T) and increased tidal volume group (IV_T) in study IV. Time zero value was measured before the increased tidal volume or PEEP was added.

	Groups	0 min	5 min	Difference	%
SV (ml min^{-1})	NV_T	59 ± 6.6	47 ± 9.2	12 ± 8.0	21
	IV_T	68 ± 11	63 ± 9.8*	4.8 ± 5.8*	7*
CO (l min^{-1})	NV_T	4.16 ± 0.92	2.76 ± 0.57	1.41 ± 0.56	33
	IV_T	4.41 ± 0.85	4.14 ± 0.96*	0.27 ± 0.77*	5*

Values of SV and CO are mean ± SD, (n = 10 in each group). At time zero the two groups were statistically similar. Cardiac output and stroke volume decreased significantly less in the IV_T group compared to the NV_T group. Independent two-tailed t-test (*, $P < 0.05$).

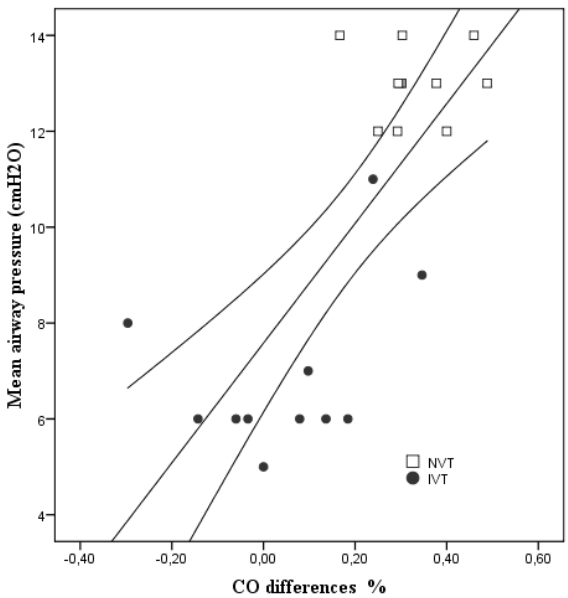

Figure 3 Correlation between the difference in cardiac output (CO) before and 5 minutes after introduction of different mode of ventilation and mean airway pressure in patients ventilated with normal tidal volume with PEEP 10 cmH_2O applied (NV_T) and increased tidal volume without PEEP (IV_T). The filled circles correspond to the IV_T group and the open squares the NV_T group, (n = 10 in each group). There was a correlation between cardiac output differences and lung mean pressure, $r^2 = 0.55$. Linear regress, ($P < 0.05$). Curved lines on each side of regression line show 95% confidence interval of the line Note: The monitor gave values for mean airway pressure as integers without decimals.

Discussion

In our system for controlled ventilation with low flow anaesthesia, we used a flexible corrugated hose between the Y-piece of the anaesthesia circle system and the endotracheal tube, a safe and simple technique described by Luttropp and Johansson.[23] The flexible corrugated tube allows adjustment of the apparatus dead space volume and the rebreathing of carbon dioxide enabling isocapnic ventilation with constant respiratory frequency despite variations in V_T.

We have in four papers, studied if large V_T achieved this way, affects elimination of carbon dioxide and/or uptake of oxygen and anaesthetic gas. The studies included both normal- and overweight patients with and without PEEP. In the absence of PEEP the difference between P_aCO_2 and $P_{ET}CO_2$ was lower in the groups with the larger V_T and in three of four studies the uptake of both oxygen and sevoflurane was higher. We found a smaller effect on cardiac output by the ventilation mode in patients ventilated with large tidal volumes than in patients ventilated with PEEP.

Influence of tidal volume on carbon dioxide elimination

In study I-III, the analysis of P_aCO_2, demonstrates lower values in the groups with larger V_T which resulted in a decrease in the P_aCO_2-$P_{ET}CO_2$ difference. In study IV, PEEP of 10 cm H_2O was applied to the NV_T group in order to prevent regions with abnormal ventilation/perfusion. In this study the difference between the P_aCO_2 and $P_{ET}CO_2$ values in the groups did not reach statistical significance and the P_aCO_2 value did not change from baseline in either group.

The findings in the IV_T groups (studies I-III) could be the result of a decreased shunt due to recruitment of lung tissue. In study IV, the P_aCO_2 value after 60 min did not differ from baseline in either group but in study III we found a greater reduction in the P_aCO_2 value. These findings may be explained, at least in part, by that in study IV mean V_T in the IV_T group was 8.6 ml kg^{-1} body weight compared to 9 - 11 ml kg^{-1} in the other three studies resulting in a smaller CO_2 elimination in study IV. This may be a shortcoming in our method using an increase in plateau pressure in order to increases the tidal volume instead of using a fixed ml kg^{-1}.

Because of a probably smaller chest wall compliance our approach may result in lower V_T increase in overweight patients compared to normal weight patients.

Tsuman and colleagues showed a decrease in the P_aCO_2–$P_{ET}CO_2$ gradient in pigs after application of PEEP, an observation also made in humans.[33-35] This suggests that the P_aCO_2-$P_{ET}CO_2$ difference is dependent on the FRC. Thus, indirect evidence for an increase in FRC in the group with larger V_T compared to the NV_T group comes from the fact that the arterial-end tidal CO_2 difference was smaller in all patients ventilated with larger V_T which is in line with previous studies.[36, 37]

Influence of tidal volume on oxygen uptake

In study II-IV, all patients had similar initial S_aO_2 and P_aO_2 levels. However, after 5 minutes after the application of the different ventilator modes, both P_aO_2 and S_aO_2 were significantly increased in the IV_T group compared to the NV_T group.

As discussed above, the CO_2 data strongly suggests recruitment of ventilated lung tissue in the IV_T group. The recruitment increases FRC.

In overweight patients FRC is lower than in patients with normal weight.[3] A low FRC increases atelectasis development, which is a plausible explanation for the existence of regions with low ventilation/perfusion ratio during anaesthesia.[1, 2] Hedenstierna and colleagues concluded that airway closure and thereby ventilation to perfusion mismatch can be prevented with increasing FRC with PEEP.[13] However, Futier and colleagues recently showed that although PEEP improves the end-expiratory lung volume after anaesthesia induction P_aO_2 remains unchanged.[25] The effect of added PEEP alone in obese patients is controversial, since several studies have demonstrated that in order to improve oxygenation a recruitment manoeuvre is needed before the application of PEEP.[38-41]

Edmark and colleagues showed that preoxygenation with 100% O_2 results in an increased formation of atelectasis.[42] To preoxygenate our patients we used 100% oxygen for 3-4 minutes with a fresh gas flow of 5 liters minute^{-1}. Lower F_iO_2 during preoxygenation or a recruitment manoeuvre after intubation might eliminate the differences in oxygenation between our groups in study IV, where PEEP was found to be inferior to large V_T concerning oxygenation.

In the study I, we found a trend towards increased arterial oxygenation levels which, however, was not statistically significant. These small differences of arterial oxygenation in the first study may be due to patient selection and/or that study methodology differed from the other studies. The patients were mostly male, anaesthetised for urological surgery. It is unlikely though that the difference in oxygenation depends on the patient selections or on a Type II error. The reason

could be a higher initial F_iO_2 in this study. Consequently, the value of S_aO_2 in the NV_T group in study I is slightly higher than in the NV_T groups in study II-III.

The patients ventilated with large V_T had lower P_aCO_2 levels. This causes a leftward shift of the oxygen-haemoglobin dissociation curve, which enhances the binding of oxygen to haemoglobin. Together with higher P_aO_2 this effect of CO_2 could contribute to the statistically significantly higher S_aO_2 in patients of the IV_T groups.

Influence of tidal volume on sevoflurane uptake

In the present studies (paper II-IV), $P_a$sevo was found to be higher in the IV_T groups compared to in the NV_T groups. $F_i$sevo did not differ between the groups. Thus, differences in inspired concentrations could be ruled out as an explanation for the higher sevoflurane uptake in the IV_T groups and it is reasonable to assume that also this finding depends on recruitment of ventilated lung tissue increasing uptake of sevoflurane in these groups.

In study IV, the higher arterial levels of sevoflurane in the IV_T group could also be caused by a better maintained cardiac output compared to a more profound decrease in the NV_T group with added PEEP. The uptake of sevoflurane into blood depends on cardiac output, as an increase of CO leads to a higher level of sevoflurane in the blood. Conversely, at a lower CO will sevoflurane uptake to be smaller with a resulting increased alveolar concentration of sevoflurane.[17] There was a slightly higher arterial concentration of sevoflurane in the participants of study II compared to studies III-IV. This can probably be explained by a lower bodyweight of the participants in study II compared with those who participated in studies III-IV. A higher body weight would affect sevoflurane concentration in the blood negatively, partly through an increased number of collapsed alveoli and partly through an increased redistribution of sevoflurane in to the patients' fat tissue because of the high fat solubility of sevoflurane.[17]

P_{ET}sevo did not differ between the groups. The increase in $P_a$sevo in the IV_T group therefore resulted in a significantly smaller P_{ET}sevo-$P_a$sevo difference. The reasons underlying the P_{ET} - P_a difference have not been elucidated for sevoflurane but Landon and colleagues have thoroughly discussed the analog difference for isoflurane. They conclude that it is in part attributable to shunt.[43] Recruitment of perfused functional gas exchange units decreases the intrapulmonary shunt and therefore raises the arterial isoflurane concentration. One could speculate whether the lower ET-a difference for sevoflurane in the IV_T group results from a lower alveolar dead space fraction. This is, infact, supported by our finding that in the NV_T group the P_{ET}sevo was higher at 1 and 3 min,

which could then be a result of enrichment of P_{ET}sevo with inspired sevoflurane from the greater alveolar dead space in this group.

To achieve 1 MAC in individuals with the average age of 60 years, 1.7-1.8 % sevoflurane has been found to be adequate.[44, 45] These studies used the expiratory sevoflurane concentration (P_{ET}sevo) to calculate the MAC value. In our study, expiratory sevoflurane concentration was similar between the groups while sevoflurane tensions in blood were significantly higher with larger V_T. This makes the P_{ET}sevo – $P_a$sevo difference smaller with larger V_T suggesting that $P_a$sevo, and subsequently depth of anaesthesia, might be underestimated when sevoflurane administration is directed by end tidal values in patients ventilated with large V_T.

Influence of tidal volume on lung compliance and FRC

In study I-III, we found a greater lung compliance in the groups ventilated with large V_T. In study IV, where the NV_T group had a PEEP of 10 cm H_2O applied, we found similar lung compliance in the groups, and the compliance in both groups had increased equally from the baselines levels.

The increased compliance in the IV_T groups (study I-IV) could represent recruitment as also was the case in the NV_T group with PEEP in study IV. There is a correlation between larger compliance and FRC volume found in studies using a recruitment manoeuvre followed by PEEP of 10 cmH_2O in obese patients.[38, 46] Murray and colleagues found that application of moderate PEEP (3.5 – 10 cmH_2O) increases FRC. Since gas exchange improved in both groups it seems reasonable to assume that both an increase in V_T, and PEEP increases FRC by recruitment of ventilated lung tissue due to the increase in airway pressures. Another mechanism could contribute to the increase in static compliance in the IV_T group. Since no PEEP was applied, before inspiration, the lung volume would be as low as corresponding to the lower, shallow part of the pressure-volume curve. After inspiration of a small V_T, the lung volume will still be in the shallow low-compliance part of the curve. After inspiration of a larger VT, however, the lung volume will appear further up at a steeper part of the pressure-volume curve. This will result in a greater static compliance.

Despite a similar increase in compliance in both groups in study IV, the plateau and mean airway pressure was lower in the IV_T group. This could be of importance since Puybasset and colleagues describe that in patients with lung injuries the addition of PEEP results in an overdistension of the upper lung lobes while in the lower lobes there is only a minor preventive effect on the formation

of atelectasis. They also report that the reopened atelectases in the lower lung parts were mostly inflammatory and less of a mechanical cause.[47]

An increase in auto-PEEP due to air trapping secondary to the larger V_T could be contribute to our results. However our monitoring system was not designed to measure such a phenomenon.

Influence of tidal volume on airway pressure

The patients in the IV_T group, in all studies received a tidal volume of 9.7 ± 2.0 ml kg^{-1} (mean ± SD) total weight corresponding to 11 ± 1.3 ml kg^{-1} predicted weights according to Lemmens formula for estimating of ideal body weight.[19] The patients in the NV_T groups received an average tidal volume of 5.4 ± 0.80 ml kg^{-1} total weight (6.4 ± 0.83 ml kg^{-1} predicted weight).

In overweight patients ventilated without PEEP (study III) plateau pressure did not differ statistically significantly between the NV_T and IV_T groups but median airway pressure was higher in the IV_T group compared with the NV_T group. Interestingly, in study IV in which the NV_T group had a PEEP of 10 cmH_2O applied, the relationship in mean airway pressure was reversed. Gammon and colleagues as well as Anzueto and colleagues found that even using normal ventilation mode to ventilate patients with lung diseases, barotrauma (e.g. pnemothorax) could develop.[48, 49] Furthermore, Boussarsar and colleagues found that the risk of barotrauma in patients with lung injury increases with higher pulmonary plateau pressures and/or decreased lung compliance.[50] They also found a weak correlation with increased V_T. Eisner and colleagues demonstrated an association between barotrauma and high inspiratory airway pressure both with and without PEEP.[51] Several other studies have addressed the influence of V_T on pulmonary inflammatory response but taken together the results are inconclusive.[52-55]

In overweight patients ventilation with large V_T created similar pulmonary plateau pressures as with normal V_T without PEEP but lower in the presence of PEEP. It thus cannot be excluded that at least in our patients, who had no signs of pulmonary disease, a moderate increase of V_T in fact constitutes a lower risk of barotrauma than application of 10 cmH_2O PEEP.

Influence of tidal volume on cardiac output

In study IV, the patients' stroke volume and cardiac output decreased less in the IV_T group than in the NV_T group, probably because of a smaller increase in intrathoracic pressure and therefore smaller effect on preload of the heart. The less

pronounced decrease in cardiac output in the IV_T group compared to the NV_T group could have a positive impact on the circulation of hypo- and normovolemic patients.[11, 12] It is interesting to note that the cardiac output was better preserved in the IV_T group despite a higher arterial sevoflurane tension in this group, since the anaesthetic in fact produces a concentration-dependent depression of cardiac output.[56]

Conclusions

The major findings of the present studies comparing patients without pulmonary and cardiovascular disease ventilated with normal tidal volumes with patients ventilated with larger tidal volumes with isocapnia accomplished with an increased apparatus dead space are:

1. Larger tidal volumes decrease the arterial-endtidal carbon dioxide gradient, and improve the oxygen and sevoflurane uptake into arterial blood in normal and overweight patients.
2. Larger tidal volumes result in lower airway plateau and mean pressures compared to normal tidal volumes with added PEEP in overweight patients.
3. Larger tidal volumes preserve cardiac output better compared to normal tidal volumes with added PEEP in overweight patients.

Acknowledgements

I would like to express my gratitude to:

Mikael Bodelsson, my tutor. For your positive attitude and continuous support and for introducing me to a scientific approach.

Anders Johansson, my co-tutor. For your positive attitude and continuous support and for your encouragement and help with the work of these studies.

Former and present heads of the Department of Intensive and Perioperative Care, Skanes University Hospital Lund, Görel Nergelius and Bengt Roth, for continuous support.

Louise Walther Sturesson, for support and for teaching me in the technique for analysis of gases with a gas chromatograph.

Michelle Chew, for support and your help to investigate the participants in study IV with trans-oesophageal echocardiography.

Åke Mellström for your positive attitude and support.

The staff at the Department of Intensive and Perioperative Care, Skanes University Hospital Lund. For encouragement and help with the practicals in study I-III.

The staff at the Department of Anaesthesia, Skanes University Hospital Malmoe. For encouragement and help with the practicals in study IV.

Last but not least, my wonderful family, Marie, Veronika, Markus and Rebecka. You are what make life important.

Populärvetenskaplig sammanfattning

Intubationer (nedsättande av andningsslang i luftstrupen) i samband med generella anestesier kan påverka lungfunktionen med en sänkt arteriell syresättning (S_pO_2) som följd. Medel för inhalationsanestesi administreras och elimineras via andningsvägarna. Anestesimedlen tas upp i blodet från lungans alveoler genom diffusion och transporteras löst i blodplasma till hjärnan där effekten för anestesi uppkommer. Lösligheten i blod för de olika anestesimedlen är den faktor som inverkar mest på den initiala farmakokinetiken. Ju lägre lösligheten för ett anestesimedel är desto fortare kommer den alveolara koncentrationen att stiga och omvänt för de lösligare anestesimedlen. Den initiala alveolara koncentrationsstegringen bestäms av den funktionella residualkapaciteten (FRC) i lungorna, den alveolara ventilationens (V_A) storlek samt den inspiriatoriska koncentrationen. När gaskoncentrationen stiger i alveolerna kommer ytterligare stegring av koncentrationen i stor utsträckning att styras av upptaget i blodplasman som avgörs av storleken på hjärtminutvolymen och lösligheten i blod.

Faktorer som påverkar FRC negativt är lägesförändringen av patienten från ett sittande/stående läge till liggande, detta reducerar FRC med en volym av 0,8-1,0 liter. Vid en anestesiinduktion försämras FRC ytterligare med en volym av 0,4-0,5 liter, detta genom att anestesifarmaka påverkar bröstkorgens muskeltonus och diafragmavalvet får en förskjutning mot bröstkorgen. Sänkta FRC volymer minskar avståndet till lungornas residualvolym, detta gör att luftvägsavstängningar inträffar lättare vid små lungvolymer. Luftvägsavstängningar är en trolig förklaring till de regioner med en låg ventilations - perfusionskvot (låg V_A/Q) som uppstår under en anestesi. Intubationen minskar den naturliga del av luftvägarna som inte deltar i patientens gasutbyte (fysiologiskt dead-space) och minskar därigenom lungornas fysiologiska residual kapacitet (FRC), vilken utgör en viktig del av lungornas syrgasreserv. Andra troliga orsaker till sänkt S_pO_2 under narkos är sammanfallen lungvävnad (atelektaser). Detta innebär en ytterligare förlust av funktionell lungvävnad och reduktion av FRC, vilket sammantaget även anses orsaka en omfördelning av blod ifrån patientens bröstkorg. Kraftigt överviktiga personer har

ett FRC och en expiratorisk reserv volym (ERV) som är reducerat vilket ytterligare förvärras vid ett liggande kroppsläge och under en anestesi.

Med denna kunskap som underlag har vi undersökt hur större andetagsvolymer (tidalvolymer), kan förbättra patientens S_pO_2 under generell anestesi. För att kunna ventilera patienterna med större andetag utan att koldioxidhalten I blodet blir för låg måste patienterna återandas en del av andetaget (dead-space andning). I de olika studierna var patienterna i de olika grupperna normal- eller överviktiga. I ventilationsmönstret på narkosapparaten ställdes in så att patientgrupperna antingen fick stora andetagsvolymer med inget positivt slut-ut-andningstryck (PEEP) eller normala andetagsvolymer med eller utan PEEP. Patienterna i de olika grupperna av normalventilerade patienter utan tillägg av dead-space och andetagsvolymer, utan PEEP (studie 1-3) eller med PEEP (studie 4) där, patienten erhöll ett PEEP på10 cmH_2O. I de olika grupperna med förstorade andningsvolymer, erhåller patienterna extra dead-space volymer, placerat mellan anestesiapparatens slangsystem och patientens trachealtub (slang placerad i luftstrupen) och större andetagsvolym. Specifik dead-space volym för varje patient genereras ur använd ventilationsmetod. Ventilationsmetoden innebär ventilation av patienterna med tidalvolymer stora nog att generera ett paustryck i lungorna (sluttryck i alveolerna), på 0.04 $cmH_2O\ kg^{-1}$ över initialt paustryck uppmätt i ventilatorn.

Resultatet som studien visade var ett måttligt högre S_pO_2 och en minskad skillnad mellan blodets koldioxid tryck (P_aCO_2) och det utandande koldioxid halten ($P_{ET}CO_2$) i den grupp som hade de större andetagen/minut-volymerna med apparat dead-space (Studie 1).

Vi har även undersökt om större tidalvolymer, genom ökad dead-space ventilation på intuberade patienter under generell anestesi åstadkommer en förändring av relationen mellan inställd mängd syrgas/sevofluran och den pulmonella/arteriella halten syrgas/sevofluran hos normal- eller överviktiga patienterna (Studie 2-3). Resultatet av dessa studier visade att det finns, en ökad blodkoncentration sevofluran i gruppen med de större andetagsvolymerna med en extra dead-space volym. Dessa studier med en ökad ventilation med ett extra dead-space volym har kunnat visa på en positiv ökning av inflödet av anestesimedlet sevofluran in i blodet och en förbättrad syresättning av patienter med större andetagsvolymerna.

I studie 4 fann vi att större tidalvolymer jämfört med normala tidalvolymer med ett tillägg av PEEP på 10 cmH_2O, gav ett ökat upptag av blodkoncentration sevofluran i gruppen med de större andetagsvolymerna med en extra dead-space volym samt en mindre sänkning av hjärtminutvolymen jämfört med den gruppen av patienter som var normalventilerade med ett tillägg av PEEP. Ett resultat som studie 4 också gav var att ventilation med större tidalvolymer gav ett lägre paus- och medeltryck I lungorna jämfört med PEEP gruppen vid anestesi av överviktiga

patienter. Ventilation med större tidalvolymer skulle alltså kunna medföra en större cirkulatorisk stabilitet genom en mindre sänkt hjärtminutvolym och en mindre risk för att få en tryckrelaterad lungskada.

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Paper I

Journal of Clinical Anesthesia (2008) **20**, 170–174

ELSEVIER

Journal of Clinical Anesthesia

Original contribution

The effect of increased apparatus dead space and tidal volumes on carbon dioxide elimination and oxygen saturations in a low-flow anesthesia system

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Received 20 October 2006; revised 4 September 2007; accepted 21 September 2007

Keywords:
Airway;
Anesthesia;
Anesthetics;
Carbon dioxide;
Gas exchange;
Lung, dead space;
Lung, volume;
Ventilation;
Ventilation-perfusion

Abstract

Study objective: To determine if a large tidal volume (V_T), with an unchanged end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$), could improve arterial carbon dioxide elimination, oxygen saturation (Sp_{O_2}), and arterial blood oxygenation.

Design: Prospective, randomized, clinical study.

Setting: Single university hospital.

Patients: 60 ASA physical status I and II patients scheduled for elective urologic or general surgery.

Interventions: Patients were randomly assigned to one of two treatments: patients in group 1, nondead space (NDS), received a fresh gas flow of 1 L/min without added apparatus dead space volume. Patients in group 2, dead space (DS), received ventilation using an added dead space volume between the Y-piece and tracheal tube. In both groups, patients' lungs were ventilated to a fixed $P_{ET}CO_2$ value of 33.8 mmHg. Patients in the DS group were ventilated with V_Ts to maintain an airway plateau pressure ($P_{plateau}$) of 0.04 cm H_2O/kg over initial plateau pressure. The corrugated tube was then adjusted to maintain a fixed $P_{ET}CO_2$.

Measurements: Dead space volumes, $P_{ET}CO_2$, arterial CO_2 tension (Pa_{CO_2}), SpO_2, arterial O_2 tension (Pa_{O_2}), V_Ts, and airway pressures were measured.

Main Results: Arterial CO_2 tension was significantly lower in the DS group, 36 ± 2.3 mmHg, compared with the NDS group, 37.5 ± 2.3 mmHg ($P < 0.05$), and the difference between $P_{ET}CO_2$ and Pa_{CO_2} was lower in the DS group than in the NDS group ($P < 0.001$). Oxygen saturation was 99% ± 1.0% in the DS group compared with 98.5% ± 1.5% in the NDS group ($P < 0.05$). Arterial O_2 tension was 13.2 ± 25.5 mmHg in the DS group and 119.1 ± 30.2 mmHg in NDS group (not significant).

Conclusion: Larger V_Ts, with an unchanged $P_{ET}CO_2$ concentration created by an added apparatus dead space volume, improved arterial carbon dioxide elimination.

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doi:10.1016/j.jclinane.2007.09.013

1. Introduction

Pulmonary gas exchange is frequently reduced with mechanical ventilation during general anesthesia. During general anesthesia patients in the supine position often have reduced arterial blood oxygenation (Pa_{O_2}) because of decreased functional residual capacity (FRC). Other major causes of reduced Pa_{O_2} are collapse of lung tissue (atelectasis) and airway closure [1]. Lung volume is reduced during general anesthesia, muscle paralysis, and mechanical ventilation, as a result of the cranial shift of the diaphragm and reduction in the thoracic transverse area. The decrease in thoracic volume is a result of a reduction in FRC and a displacement of blood from the thorax to the abdomen [2].

There is a relationship between airway closure and perfusion of poorly ventilated lung regions [3]. Hedenstierna and colleagues [1] concluded that airway closure and thereby the ventilation to perfusion mismatch, can only be prevented with increasing FRC with positive end-expiratory pressure (PEEP). With this background, we sought to determine if larger tidal volumes (V_Ts), with an unchanged partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) and inspired oxygen concentration (F_{IO_2}), would improve arterial CO_2 elimination and Pa_{O_2}.

2. Materials and methods

The study was approved by the University of Lund Hospital (Lund, Sweden) regional ethics committee, and written, informed consent was obtained from all patients. We studied 60 ASA physical status I and II patients who were scheduled for elective general or urologic surgery with an expected anesthesia time of two hours or more. Patients with a history of, or laboratory or physical evidence of, pulmonary or significant cardiovascular disease were excluded from the study. The 60 patients were randomly assigned to one of two treatments (30 patients in each group) via sealed envelope assignment. The lungs of patients in group 1 (nondead space [NDS]) were ventilated without an extra apparatus dead space volume. In group 2 (dead space [DS]), patients received ventilation using an added dead space volume between the Y-piece and endotracheal tube.

All patients received premedication with midazolam, 7.5 mg, orally 30 minutes before admission to the operating theater. After preoxygenation with 100% oxygen for three to four minutes and a fresh gas flow of 4.5 L/min, anesthesia was induced with fentanyl, 2 μg/kg, and propofol, 1.5 to 2 mg/kg. Rocuronium, 0.6 mg/kg, was administered for muscle paralysis. Ventilation was manually assisted with 100% oxygen via a circle system (4.5 L [vol]), until tracheal intubation, and thereafter with a ventilator (Dräger Primus; Dräger Medical, Lübeck Germany). Fresh gas flow (F_{IO_2}, 0.35 in nitrous oxide [N_2O]) was 4.5 L/min during the first 5 min and then adjusted to 1.0 L/min (anesthesia was maintained with sevoflurane, adjusted to an end-tidal concentration of 1.3%). No PEEP was used. The ventilator rate was 15 breaths per minute, inspiratory-expiratory ratio was 1:2 (including inspiratory pause of 10%). In the DS group, an adjustable corrugated tube (single-use plastic tube, Medcore AB, Uppsala, Sweden) was placed between the Y-piece and the heat and moisture exchanger. In the NDS group, no adjustable tube was used. Patients in the NDS group received ventilation with V_Ts adjusted to obtain $P_{ET}CO_2$ pressure of 33.8 mmHg. Before each anesthetic administration, fresh soda lime (Drägersorb, Dräger Medical, Lübeck, Germany) was used, and end-tidal inspired carbon dioxide (F_{ICO_2}) was measured to detect rebreathing. Patients in the DS group were ventilated with V_Ts to achieve ventilator plateau pressure ($P_{plateau}$) of 0.04 cm H_2O/kg over initial measured plateau pressure. The corrugated tube was then adjusted to maintain $P_{ET}CO_2$ pressure of 33.8 mmHg. We measured dead space volumes in the DS group by filling the tube with water, then measuring this volume of water.

Monitoring during the procedure included three-lead electrocardiography, heart rate, invasive arterial pressure (measured in the radial artery), and oxygen saturation by pulse oximetry (Sp_{O_2}). Inspired oxygen and end-tidal concentrations of sevoflurane, N_2O, and CO_2 were monitored at the distal end of the tracheal tube throughout the two-hour study time, and analyzed gases were returned to a port fitted into the CO_2 absorber. The $P_{ET}CO_2$ values were measured and analyzed by the Primus anesthetic machine using a sidestream technique with 150 mL flow and response time less than 500 ms (Dräger Primus, Dräger Medical, Lübeck, Germany). Arterial blood oxygenation was sampled from the arterial cannula, then measured every 15 minutes using an automated analyzer (ABL 725, Radiometer, Copenhagen, Denmark).

Additional doses of fentanyl were administered if mean blood pressure increased more than 20% from baseline. Decreases in blood pressure were treated with intravenous (IV) ephedrine, 5 to 10 mg. Neuromuscular block was maintained with rocuronium IV, and supplementary doses were given when two twitches were reached with a neuromuscular transmission analyzer (TOF-Watch; Organon Teknika BV, Boxtel, The Netherlands).

Table 1 Demographic data of the NDS and DS groups

	NDS (N = 29)	DS (N = 30)
Age (yrs)	63 ± 14	61 ± 13
Men-Women ratio	23:6	21:9
Weight (kg)	82.6 ± 12.5	78.9 ± 15.2
BMI (kg/m^2)	27.6 ± 3.4	25.8 ± 3.3
Smoker	2	3

Values are means ± SD. There were no statistical differences between the groups in age, gender, body mass index (BMI), weight, or smoking status (smoker).

Table 2 Comparison of tidal volumes (V_Ts), ventilator peak pressure (P_{peak}), ventilator plateau pressure ($P_{plateau}$), and inspired carbon dioxide concentration ($FICO_2$) between the dead space (DS) and non dead space (NDS) groups

		15 min	60 min	120 min
V_T (mL)	DS	742.20 ± 93.9 *	739.2 ± 110 *	745.8 ± 121.3 *
V_T (mL)	NDS	456.60 ± 84.4	468.8 ± 80.9	485.0 ± 79.8
P_{peak} (cm H_2O)	DS	26.90 ± 4.1 *	28.23 ± 4.0 *	29.1 ± 3.9 *
P_{peak} (cm H_2O)	NDS	18.27 ± 6.0	19.17 ± 5.4	20.1 ± 5.2
$P_{plateau}$ (cm H_2O)	DS	15.67 ± 3.0 **	16.97 ± 3.2 ***	18.13 ± 3.1 *
$P_{plateau}$ (cm H_2O)	NDS	13.70 ± 4.0	14.9 ± 3.3	15.03 ± 3.2
$FICO_2$ (mmHg)	DS	1.5 ± 0.8	1.5 ± 0.8	1.5 ± 0.8
$FICO_2$ (mmHg)	NDS	0.8 ± 0.0	0.8 ± 0.0	0.8 ± 0.0

Values are means ± SD.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

2.1. Statistical analysis

All data are reported as mean values ± SD. A power analysis showed that when assuming an arterial O_2 difference at 15 mmHg with a DS of 7.5 mmHg, 30 patients in each group would be needed for a power of 0.85 at $P < 0.05$. A Gaussian distribution test was done before the *t* test. Demographic data were analyzed using the unpaired, two-tailed *t* test (body mass index [BMI], weight, age), χ^2 test (male-female), and Fisher's exact test (smoking). Dead space volumes, ventilator plateau pressures, V_Ts, SpO_2, PaO_2, and $PaCO_2$ were analyzed using the unpaired, two-tailed *t* test. All statistical analysis was performed using SPSS statistical computing program (SPSS version 12.0, SPSS, Chicago, IL).

3. Results

All surgical procedures had an anesthesia time of more than 120 minutes. No intraoperative problems were noted during the study. All patients recovered uneventfully from anesthesia and were discharged from the hospital in accordance with normal practice for their respective surgical procedures. One patient from the NDS group was excluded from the study after 90 minutes because of a period of desaturation of SpO_2 less than 90%. Demographic data showed no significant differences between the groups (Table 1).

All patients received ventilation with a FIO_2 of 0.35. Peak and plateau pressures and V_Ts were significantly higher in the DS group than in the NDS group (Table 2). The adjustable dead space volume between the Y-piece and the heat and moisture exchanger was 239 ± 95 mL in the DS group.

In the DS group, there was more rebreathing of CO_2; $FICO_2$ was 1.5 ± 0.0 mmHg in the DS group compared with 0.8 ± 0.0 mmHg in the NDS group (Table 2). End-tidal carbon dioxide partial pressure was 34.2 ± 1.5 mmHg in the DS group versus 33.7 ± 0.8 mmHg in the NDS group (not significant). Arterial carbon dioxide tension in the DS group was significantly lower (36.3 ± 2.1 mmHg) than that of the NDS group (37.5 ± 2.3 mmHg) ($P < 0.05$) (Table 3). There was a significant arterial to $P_{ET}CO_2$ difference in both groups, though the difference was smaller in the DS group (2.2 ± 1.9 mmHg) than the NDS group (4.3 ± 2.2 mmHg) ($P < 0.001$) (Table 4).

Oxygen saturation was 99% ± 1.0% in the DS group and 98.5% ± 1.5% in the NDS group ($P < 0.05$; Fig. 1, Table 3).

Table 3 Comparison of PaO_2, SpO_2, $P_{ET}CO_2$, and $PaCO_2$ between the dead space (DS) and non dead space (NDS) groups

		15 min	60 min	120 min
SpO_2 (%)	NDS	97.73 ± 2.36	97.30 ± 2.53	98.45 ± 1.53
SpO_2 (%)	DS	98.70 ± 1.73 *	98.13 ± 1.74 **	98.97 ± 1.00 *
PaO_2 (mmHg)	NDS	117.2 ± 34.7	113.3 ± 36.3	119.1 ± 30.2
PaO_2 (mmHg)	DS	132 ± 30.1	123.3 ± 30.6	132.2 ± 25.7
$P_{ET}CO_2$ (mmHg)	NDS	32.6 ± 2.3	33.8 ± 1.1	33.7 ± 0.8
$P_{ET}CO_2$ (mmHg)	DS	33.8 ± 2.5	33.7 ± 1.1	34.2 ± 1.2
$PaCO_2$ (mmHg)	NDS	37.5 ± 2.5	38.5 ± 1.8	37.5 ± 2.3
$PaCO_2$ (mmHg)	DS	36 ± 2.8 *	36 ± 1.9 ***	36.3 ± 2.1 *

Values means ± SD. There were no statistical differences between the groups in PaO_2 or $P_{ET}CO_2$.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

Table 4 Comparison of differences between Pa_{CO_2} and $P_{ET}CO_2$ in the dead space (DS) and non dead space (NDS) groups

	15 min	60 min	120 min
DS (mmHg)	2.3 ± 2.1 *	2.3 ± 1.7 *	2.1 ± 1.9 **
NDS (mmHg)	4.7 ± 2.1	4.7 ± 1.9	3.8 ± 2.3

Values are means ± SD.
* $P < 0.001$.
** $P < 0.01$.

Arterial oxygen tension was 132 ± 25.5 mmHg in the DS group and 119 ± 30 mmHg in the NDS group (not significant) (Table 3).

4. Discussion

We tried an easy, practical way of increasing the V_T ventilation, and thus FRC, without changing $P_{ET}CO_2$, so as to decrease ventilation-perfusion (VA/Q) mismatch. This was done by adding a dead space volume, an adjustable tube, between the Y-piece and the heat and moisture exchanger [4]. Scott and colleagues [5,6] described a variable apparatus dead space method designed to maintain normocapnia despite overventilation. However, in their study the mixing of gases was dependent on a number of factors. Our study is different in that the amount of functional dead space was not dependent on rate of fresh gas flows.

In this study, during low-flow anesthesia, the extra dead space volume was used for at least two hours of anesthesia. The main results show a significantly lower Pa_{CO_2}, with a slight improvement of Sp_{O_2}, values in the DS group, although the Pa_{O_2} difference between the groups was statistically insignificant. Although there was a statistical difference in Pa_{CO_2} between the groups, this difference may be accounted for by the measurement error in the blood gas analyzer alone and may be not clinically significant.

Fletcher and Jonson [7] found that the arterial CO_2 versus $P_{ET}CO_2$ difference was inversely related to V_Ts in anesthetized patients whose lungs were ventilated with varying respiratory rates but also with constant alveolar ventilation. Their study showed a median arterial CO_2 versus $P_{ET}CO_2$ difference of 4.5 mmHg at small volumes versus 2.3 mmHg at larger V_Ts. Whiteley et al [8] confirmed these findings, that breathing patterns with longer inspiratory times yield lower values of arterial P_{CO_2}. Based on the Enghoff modification of the Bohr equation, dead space volumes increased with increasing pulmonary shunt (Appendix) [9,10]. In our study, the DS group showed a smaller difference in Pa_{CO_2} versus $P_{ET}CO_2$ compared with the NDS group. Therefore, in relation to the Enghoff modification equation and the findings of Fletcher and Jonson, our study supports the theory that the increased alveolar ventilation probably occurred because the mean arterial CO_2 versus $P_{ET}CO_2$ difference was lower in the DS group.

Hypercapnia increases cardiac output, decreases systemic vascular resistance and oxygen extraction, and increases oxygen availability to tissue [11]. Mild intraoperative hypercapnia is known to increase subcutaneous and cerebral oxygenation. By provoking local subcutaneous vasodilatation, Akca et al [12] showed that tissue P_{O_2} was greater in mildly hypercapnic patients. In our study, Sp_{O_2} values in the DS group were significantly higher than in the NDS group. These findings may indicate an improved peripheral oxygenation, which could be ascribed to a smaller alveolar shunt. Our finding is consistent with those of Sykes et al [13] and Visick et al [14] that showed that larger V_Ts improved Pa_{O_2}. However, our results must be interpreted with caution because the Sp_{O_2} value was significantly increased without significantly improved Pa_{O_2}. A larger sample of patients might show a significant difference in Pa_{O_2} between the groups.

The present method may be considered controversial insofar as increased V_Ts may increase the risk of barotrauma and volutrauma. However, we believe that this method corresponds well to different patients' thoracic compliance. The adjustable dead space volumes in the DS group were 239 ± 95 mL and reflect the variation of the different body weights and BMI. The method used in this study, with a $P_{plateau}$ of 0.04 cm H_2O/kg over the initial plateau pressure, yielded a maximum $P_{plateau}$ in the DS group of 18 to 21 cm H_2O and corresponded with a $P_{plateau}$ of 15 to 18 cm H_2O (NDS group) with a PEEP of 5 cm H_2O. The rationale for the present target of plateau pressure in this study is based on the study of Johansson et al [4], which determined that larger V_Ts decreased CO_2 temperatures during low flow and minimal flow. Using their data, we calculated the plateau pressure that was used in our study.

It is true that alveolar recruitment can be achieved not only by PEEP or higher plateau pressures. In an animal study, Syring et al [15] recently described different ventilatory rates and high-frequency ventilation modes as an alternative to this issue of alveolar recruitment. However, their study was conducted in lung-injured animals, and the

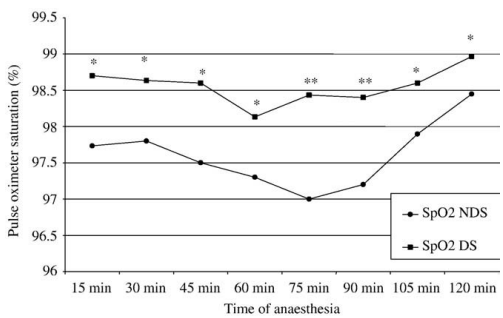

Fig. 1 Comparison of oxygen saturation, as measured by pulse oximeter, between the dead space (DS) and the non dead space (NDS) volume groups. All values are expressed as means ± SD. *$P < 0.05$, **$P < 0.01$.

lung mechanics are therefore completely different. Oscillatory mechanisms, for example, become more important in this setting; we think that there are lesser mechanisms in healthy lungs. The above-described method, $P_{plateau}$ of 15 to 18 cm H_2O (NDS group) with a PEEP of 5 cm H_2O, is commonly used in general anesthesia. According to the V_Ts used in the DS group, patients were not ventilated with V_Ts above 10 mL/kg. We believe that all patients were ventilated within safe limits, both with regard to volume and pressures.

We were unable to detect a beneficial improvement in Pa_{O_2} in this study. However, we found that larger V_Ts, created by increased apparatus dead space volumes, improved arterial CO_2 elimination with a minor increase in Sp_{O_2}.

Appendix A

The Enghoff modification of the Bohr equation:

$$V_{Dphysiol}/V_T = (Pa_{CO_2} - PÉ_{CO_2})/Pa_{CO_2}$$

where $V_{Dphysiol}$ = dead space, V_T = tidal volume, Pa_{CO_2} = arterial carbon dioxide tension, and $PÉ_{CO_2}$ = mixed expired carbon dioxide.

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Paper II

Acta Anaesthesiol Scand 2010; **54**: 1111–1116
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2010.02291.x

Larger tidal volume increases sevoflurane uptake in blood: a randomized clinical study

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Background: The rate of uptake of volatile anesthetics is dependent on alveolar concentration and ventilation, blood solubility and cardiac output. We wanted to determine whether increased tidal volume (V_T), with unchanged end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$), could affect the arterial concentration of sevoflurane.
Methods: Prospective, randomized, clinical study. ASA physical status ^{2} and II patients scheduled for elective surgery of the lower abdomen were randomly assigned to one of the two groups with 10 patients in each: one group with normal V_T (NV_T) and one group with increased V_T (IV_T) achieved by increasing the inspired plateau pressure 0.04 cmH_2O/kg above the initial plateau pressure. A corrugated tube added extra apparatus dead space to maintain $P_{ET}CO_2$ at 4.5 kPa. The respiratory rate was set at 15 min^{-1}, and sevoflurane was delivered to the fresh gas by a vaporizer set at 3%. Arterial sevoflurane tensions ($P_a$sevo), $F_i$sevo, P_{ET}sevo, $P_{ET}CO_2$, P_aCO_2, V_T and airway pressure were measured.
Results: The two groups of patients were similar with regard to gender, age, weight, height and body mass index. The mean P_{ET}sevo did not differ between the groups. Throughout the observation time, arterial sevoflurane tension (mean ± SE) was significantly higher in the IV_T group compared with the NV_T group, e.g. 1.9 ± 0.23 vs. 1.6 ± 0.25 kPa after 60 min of anesthesia ($P < 0.05$).
Conclusion: Ventilation with larger tidal volumes with isocapnia maintained with added dead-space volume increases the tension of sevoflurane in arterial blood.

Accepted for publication 19 July 2010

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Background

The rate of uptake of a volatile anesthetic to the blood from the alveoli is dependent on the alveolar concentration and blood solubility of the anesthetic, as well as cardiac output. The initial alveolar concentration could be enhanced by a larger functional residual capacity (FRC) initiated by positive end-expiratory pressure (PEEP), an increased alveolar ventilation and/or by an increased inspiratory gas concentration.[1,2]

The factors negatively affecting FRC are the change from a sitting to a supine position, with an FRC reduction of 0.8–1.01.[3] With the induction of anesthesia, FRC is further reduced another 0.4–0.51 by reduced chest muscle tone and cranial displacement of the diaphagram induced by the anesthetic drugs.[3,4] Reduced FRC parallels a reduced residual volume, making airway closure more frequent, which is a likely explanation for the appearance of regions with a low ventilation to perfusion ratio and atelectasis during anesthesia.[5,6] Hedenstierna[5] found, however, that airway closure can be prevented by increasing FRC using a PEEP.

We have investigated previously whether an increased tidal volume can affect arterial oxygenation and oxygen saturation during general anesthesia.[7] To allow ventilation with larger tidal volumes without causing hypocapnia, exhaled gas was rebreathed by an increased apparatus dead space. The results showed a moderately improved oxygenation but also a reduced difference between arterial and exhaled carbon dioxide tension with larger tidal volumes.[7] In patients ventilated with larger tidal volumes, the results were similar to what could be expected from an increase in FRC. We hypothesized that if larger tidal volumes were utilized, the arterial concentration of a sevoflurane would increase. The aim of the present study was therefore to determine whether larger tidal volumes could affect the arterial concentration of sevoflurane in patients undergoing abdominal surgery.

Method

Patients

The study was approved by the regional Ethics committee (Lund, Sweden) according to the standards set in the Helsinki declaration. The investigation included 20 patients, ASA physical status 1 or 2, scheduled for elective colon surgery between March 2008 and February 2009 at Lund University Hospital. All procedures were estimated to last more than 60 min. Consent to participate in the study was obtained from each patient. Patients with known pulmonary or cardiovascular disease were excluded. Patients were enrolled and randomized by the responsible anesthesiologists to one of two groups with 10 patients in each group via randomly mixed sealed envelope assignment at the start of the procedure in the operating theater (Fig. 1).

Experimental procedure

Before the start of anesthesia, an unused carbon dioxide absorber was applied (Drägersorb, Dräger Medical, Lübeck, Germany) to the anesthesia circuit (Dräger Primus™, Dräger Medical). All patients were pre-oxygenated with 100% oxygen for 3–4 min with a fresh gas flow of 5 l/min. Anesthesia was induced with 2 μg/kg fentanyl and 1.5–3.0 mg/kg propofol. Atracurium 0.6 mg/kg was administered for muscle paralysis. Ventilation was assisted manually with 100% oxygen via a semi-open circle system (4.5 l volume) until tracheal intubation and then by means of a ventilator with a FiO_2 at 0.35 in nitrogen. No PEEP was applied. Propofol 8 mg/kg/h was infused until an arterial cannula had been inserted into the radial artery.

In the group with a normal tidal volume (NV_T), the respiratory rate was set to 15 min^{-1} and V_T was adjusted as to achieve a $P_{ET}CO_2$ at 4.5 kPa. In the group with increased tidal volume (IV_T), the respiratory rate was set to 15 min^{-1}. The initial plateau pressure ($P_{plateau}$) was monitored and then V_T was increased until $P_{plateau}$ was 0.04 cm H_2O/kg above the initial $P_{plateau}$. The $P_{ET}CO_2$ was then adjusted to 4.5 kPa with a flexible corrugated hose (disposable plastic tube, Medcore, AB Uppsala, Sweden) placed between the Y-piece of the anesthesia circle system and the heat and moisture filter (HME) attached to the endotracheal tube.[7,8] This flexible corrugated hose increased the dead-space volume and provided adjustable rebreathing of carbon dioxide. In both groups, the inspiratory : expiratory ratio was 1 : 2, including an inspiratory plateau of 10%. When stable $P_{ET}CO_2$ values reached 4.5 kPa, a control (time zero) sample of arterial blood was obtained and sevoflurane administration was started using a vaporizer. The sevoflurane concentration was set to 3% on the vaporizer, and after 5 min, the fresh gas flow was adjusted to 1.0 l/min with an unchanged sevoflurane concentration throughout the anesthesia period.

Blood samples of 3 ml were drawn from the arterial line into heparinized syringes at 0, 1, 3, 5, 10, 15, 30, 45 and 60 min after the start of the sevoflurane administration (total 27 ml). Arterial oxygen tensions (PaO_2), oxygen saturation (SaO_2) and carbon dioxide tension ($PaCO_2$) were analyzed using an automatic blood gas analyzer (ABL 725™, Radiometer, Copenhagen Denmark). Sevoflurane concentration was analyzed using gas chromatography (GC) on a Perkin-Elmer 3920 gas liquid chromatograph (Perkin-Elmer 3920 gas liquid chromatograph, CT, USA).

Patients were monitored with three-lead ECG, invasive arterial blood pressure via the arterial cannula, SpO_2 (Intelli Vue MP70 Anesthesia, Phi-

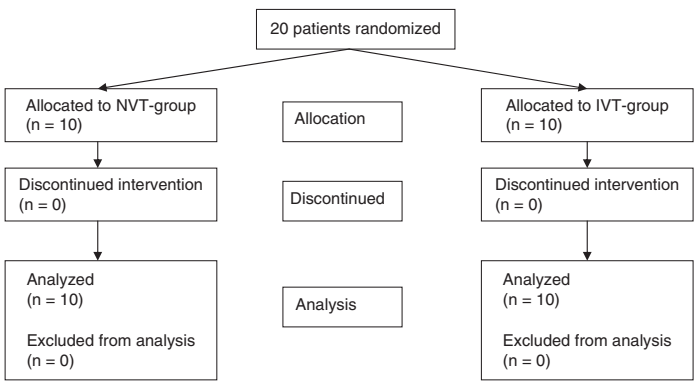

Fig. 1. Patient flow of the study.

lips Medizin System, Boeblingen, Germany), inspiratory and expiratory oxygen partial pressure (F_iO_2, $P_{ET}O_2$), sevoflurane inspiratory and expiratory partial pressure ($F_i$sevo, P_{ET}sevo) and carbon dioxide inspiratory and expiratory partial pressure (F_iCO_2, $P_{ET}CO_2$) as analyzed by the ventilator. Total ventilation per minute, tidal volumes and airway pressures such as peak pressure, plateau pressure and mean pressure were measured and documented at the same intervals. Static compliance of the respiratory system was calculated as the tidal volume divided by the inspiratory plateau pressure.

Extra doses of fentanyl (50–100 μg) were administered if the mean arterial blood pressure (MAP) increased >20% above the initial baseline level. Hypotension (MAP<60 mmHg) was treated with 5–10 mg ephedrine intravenously. All patients received 3–5 ml/kg/h of glucose 2.5% with sodium (70 mmol/l), chloride (45 mmol/l) and acetate (25 mmol/l) intravenously. Neuromuscular blockade was monitored using a neuromuscular transmission analyzer (TOF-Watch™; Organon Technology B V., Boxel, the Netherlands). Additional doses of atracurium were administered at the discretion of the anesthetist.

GC

The sevoflurane partial pressure in arterial blood was determined using the GC head space technique described by Smith et al.[9] The method yields blood sevoflurane tension as a fraction of dry gas.[9] In brief, three 0.6 l cylinders with different known tensions of sevoflurane in nitrogen were prepared and the gas mixtures were used as standards before analysis of the blood samples. The standards of sevoflurane were used to confirm the stability of the measurements and for the calculation of sevoflurane tension in the blood samples. The standard curve was linear and did not differ to any major extent between different days. Two milliliters of the blood sample was transferred to gas-tight 4.75 ml vials immediately after the collection of the 60-min sample. The blood concentration of sevoflurane was measured after equilibration for 30 min at 37 °C by injecting 50 μl of the headspace gas into the gas–liquid chromatograph using flame ionization detection.[10] Two headspace readings were obtained from every blood sample and the mean was used in the subsequent calculations. For three randomly assigned blood samples of each patient, 1 ml of the equilibrated blood was transferred into a new 4.75 ml gas-tight vial. After another 30 min equilibration at 37 °C, the headspace was analyzed. This double-headspace technique enables the calculation of the blood gas partition coefficient.[9]

Statistics

All statistical analyses were performed using SPSS 16.0 for Windows, (SPSS Inc., Chicago, IL), except for the values analyzed over time. Time-dependent data were analyzed using Sigma Stat for Windows 3.0.1 (SPSS Inc.). An initial power analysis assuming a $P_a$sevo concentration difference at 0.3 kPa with an SD of 0.2 kPa revealed that seven patients in each group would be required to achieve a power of 0.8 at $P<0.05$. Ten patients in each group were enrolled. Descriptive variables, tidal volumes and airway pressures were not normally distributed and are expressed as median and inter quartile range in square brackets and analyzed using a nonparametric method according to the Mann–Whitney test. The values of $F_i$sevo, P_{ET}sevo, $P_{ET}CO_2$ and the partition coefficient are presented as mean ± SD and the analysis was conducted using an independent two-tailed *t*-test. For the change of values over time, an analysis with a two-way repeated measurement ANOVA was used. The ANOVA analysis was then followed by the Holm–Sidak *post hoc* test when appropriate. A *P*-value <0.05 was considered to indicate statistical significance.

Results

The two groups of patients were similar with regard to gender, age, weight, height and body mass index (Table 1). No intraoperative problems were observed during the study. All patients recovered from anesthesia and left the post-operative unit in accordance with the routines assigned for the various surgical procedures.

The tidal volumes were significantly larger in the IV_T group (Table 2). The peak, plateau and mean

Table 1

Patient data.

	NV_T	IV_T
Number of patients	10	10
Women (*n*)	5	6
Age (years)	70 [61–83]	66 [42–72]
Weight (kg)	63 [58–71]	63 [47–75]
Length (m)	1.70 [1.67–1.76]	1.69 [1.54–1.79]
Body mass index (kg/m^2)	23 [19–24]	22 [19–24]

Values are median with interquartile range within brackets.

Table 2

Comparison of tidal volumes (V_T), tidal volume kg body weight^{-1}, peak, plateau, mean airway pressures and lung compliance in the increased tidal volume group (IV_T) and the normal tidal volume group (NV_T).

	5 min	30 min	60 min
V_T (ml)			
NV_T	350 [315–405]	357 [318–403]	350 [328–393]
IV_T	703 [580–763]*	706 [567–765]*	700 [550–750]*
V_T (ml/kg)			
NV_T	5.7 [4.9–6.5]	5.5 [5.3–6.5]	5.7 [5.1–6.4]
IV_T	12 [10–13]*	11 [10–13]*	11 [9.4–13]*
P_{Peak} (cmH_2O)			
NV_T	12 [11–13]	13 [11–15]	14 [12–15]
IV_T	20 [19–21]*	21 [19–22]*	21 [19–23]*
$P_{Plateau}$ (cmH_2O)			
NV_T	11 [9.8–12.3]	12 [11.0–12.0]	12 [11.0–12.0]
IV_T	16 [14–17]*	17 [15–17]*	16 [15–17]*
P_{Mean} (cmH_2O)			
NV_T	3.5 [3.0–4.3]	4.0 [3.0–4.3]	4.0 [3.8–4.3]
IV_T	6.0 [5.0–6.3]*	6.0 [5.0–6.3]*	6.0 [5.8–7.0]*
Lung compliance (ml/cmH_2O)			
NV_T	31 [28–44]	31 [28–33]	31 [28–34]
IV_T	45 [35–56]*	45 [35–51]*	44 [33–48]*

Values are median [inter quartile range], $n = 10$ in each group. All values were statistically significantly different between groups.
*$P < 0.05$.

Table 3

Comparison of the values for the expiratory carbon dioxide ($P_{ET}CO_2$), carbon dioxide pressure in arterial blood ($PaCO_2$) and $PaCO_2$–$P_{ET}CO_2$ difference (P_a–$P_{ET}CO_2$) between the normal tidal volume group (NV_T) and the increased tidal volume group (IV_T).

	5 min	30 min	60 min
$P_{ET}CO_2$ (kPa)			
NV_T	4.4 ± 0.34	4.4 ± 0.17	4.5 ± 0.07
IV_T	4.4 ± 0.18	4.5 ± 0.12	4.5 ± 0.13
P_aCO_2 (kPa)			
NV_T	5.4 ± 0.46	5.5 ± 0.34	5.7 ± 0.37
IV_T	4.9 ± 0.34*	4.9 ± 0.27*	4.9 ± 0.27*
P_a-$P_{ET}CO_2$ (kPa)			
NV_T	0.97 ± 0.32	1.02 ± 0.34	1.09 ± 0.35
IV_T	0.31 ± 0.22*	0.40 ± 0.29*	0.42 ± 0.26*

Values are mean ± SD ($n = 10$ in each group). $P_{ET}CO_2$ values were similar in the two groups. The values of P_aCO_2 and P_a-$P_{ET}CO_2$ were statistically significantly lower in the IV_T group compared with the NV_T group.
*$P < 0.05$.

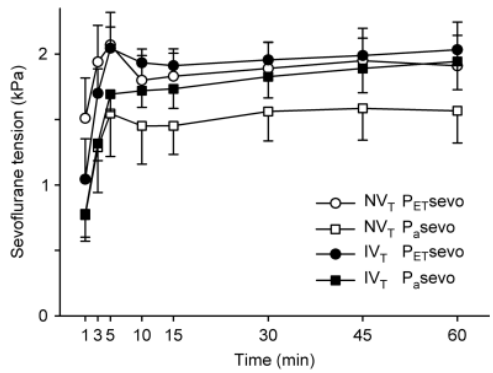

Fig. 2. Comparison of the values for arterial sevoflurane ($P_a$sevo, squares) and end-tidal sevoflurane tension (P_{ET}sevo, circles) between the increased tidal volume group (IV_T, filled symbols) and normal tidal volume group (NV_T, open symbols). Values are mean ± SD (n = 10 in each group). The expiratory sevoflurane concentration was similar in the two groups. Arterial sevoflurane tensions was significantly higher in the IV_T group compared with the NV_T group and the differences increased with time. Two-Way repeated measurement ANOVA followed by Holm-Sidak post hoc *test (P < 0.05).*

airway pressure were significantly higher in the IV_T group compared with the NV_T group (Table 2). The median adjustable dead-space volume between the Y-piece and HME in the IV_T group was 3.1 [2.6–4.1] ml/kg. Lung compliance was larger in the IV_T group throughout the observation period ($P < 0.05$, Table 2).

The mean end-tidal carbon dioxide values ($P_{ET}CO_2$) were similar in the two groups (Table 3). P_aCO_2 was lower in the IV_T group throughout the observation period ($P < 0.05$, Table 3). The difference between P_aCO_2 and $P_{ET}CO_2$ was smaller in the IV_T group compared with the NV_T group ($P < 0.05$, Table 3).

P_{ET}sevo at 1 and 3 min was higher in the NV_T group ($P < 0.05$, Fig. 2), but no statistically significant differences were found between 5 and

Table 4

Comparison of the values for the inspiratory sevoflurane concentrations ($F_i$sevo), expiratory sevoflurane concentrations (P_{ET}sevo), arterial sevoflurane tensions ($P_a$sevo) and P_{ET}-sevo-$P_a$sevo difference (P_{ET}-$P_a$sevo) between increased tidal volume group (IV_T) and normal tidal volume group (NV_T).

	5 min	30 min	60 min
$F_i$sevo (kPa)			
NV_T	2.8 ± 0.35	2.3 ± 0.20	2.4 ± 0.23
IV_T	2.7 ± 0.28	2.4 ± 0.21	2.5 ± 0.27
P_{ET}sevo (kPa)			
NV_T	2.1 ± 0.25	1.9 ± 0.20	1.9 ± 0.23
IV_T	2.0 ± 0.16	2.0 ± 0.13	2.1 ± 0.21
$P_a$sevo (kPa)			
NV_T	1.5 ± 0.37	1.6 ± 0.23	1.6 ± 0.25
IV_T	1.7 ± 0.13*	1.8 ± 0.16*	1.9 ± 0.23*
P_{ET}-$P_a$sevo (kPa)			
NV_T	0.52 ± 0.27	0.33 ± 0.21	0.34 ± 0.27
IV_T	0.34 ± 0.21*	0.14 ± ± 0.10*	0.12 ± 0.13*

Values are mean ± SD ($n = 10$ in each group). $F_i$sevo and P_{ET}sevo values were not significantly different between the groups. Arterial sevoflurane tensions were statistically significantly higher in the IV_T group compared to the NV_T group. P_{ET}sevo-$P_a$sevo differences were statistically significantly lower in the IV_T group compared to the NV_T group. Two-way repeated measurement ANOVA followed by Holm-Sidak *post hoc* test.
*$P < 0.05$.

60 min (Table 4). The mean $P_a$sevo was higher in the IV_T group compared with the NV_T group from 5 min and onwards and the difference increased with time ($P < 0.05$, Table 4, Fig. 2). The mean P_{ET}sevo did not differ between the groups. The difference between $P_a$sevo and P_{ET}sevo was smaller in the IV_T group compared with the NV_T group ($P < 0.05$, Table 4, Fig. 2).

The blood gas partition coefficient for sevoflurane was 0.68 ± 0.045.

Discussion

In the present study, the mean $P_a$sevo was found to be higher in patients ventilated with larger tidal volumes. The reason for this is not clear but could be due to an increase in inspired gas concentration, FRC and/or alveolar ventilation. The vaporizer was set to deliver fresh gas containing 3% sevoflurane to all patients and $F_i$sevo did not differ between the patients, ruling out the first explanation.

To our knowledge, there are no data on the effect of tidal volume on FRC in artificially ventilated patients. It seems, however, reasonable to assume that an increase in V_T increases FRC by the recruitment of ventilated lung tissue due to the increase in airway pressure. Murray and colleagues found that the application of moderate PEEP (3.5–10 cmH_2O) increases FRC, and Tusman and colleagues showed a decrease in the P_aCO_2–$P_{ET}CO_2$ gradient in pigs after application of PEEP, an observation also made in humans.[11–13] Thus, indirect evidence for an increase in FRC with larger V_T in our patients emerges from the fact that the arterial-end tidal CO_2 difference was smaller in the patients ventilated with larger V_T as also demonstrated previously.[7,14,15] Further evidence that our patients in the IV_T group had increased FRC emerges from their larger lung compliance. This is supported by other studies using a recruitment maneuver, followed by a PEEP of 10 cmH_2O in obese patients.[16,17]

The increase in $P_a$sevo in the IV_T-group resulted in a significantly smaller P_{ET}sevo–$P_a$sevo difference. The reasons underlying the P_{ET}–P_a difference have not been elucidated for sevoflurane but Landon and colleagues have thoroughly discussed the equivalent difference for isoflurane. They conclude that it is in part attributable to shunt.[18] The recruitment of perfused functional gas exchange units decreases the intrapulmonary shunt and improves arterial oxygenation. We have previously demonstrated that ventilation with increased V_T with maintained isocapnia increases P_aO_2 and S_pO_2.[7] This further indicates that with larger tidal volumes, recruitment indeed takes place. The lower A-a difference for CO_2 in the IV_T group could also result from a lower alveolar dead-space fraction. This is supported by our findings of a higher P_{ET}sevo in the NV_T group at 1 and 3 min because the alveolar dead space will enrich P_{ET}sevo with inspired sevoflurane to a greater extent in this group.

It cannot be ruled out that an increase in alveolar ventilation could contribute to the improved sevoflurane uptake in the IV_T group. Because of the introduction of increased apparatus dead space in the IV_T group, the alveolar ventilation with respect to CO_2 and sevoflurane is, however, not comparable between the two groups and must be evaluated separately. Thus, the alveolar ventilation with respect to sevoflurane could be increased by larger V_T.

To achieve 1 minimum alveolar concentration (MAC) in individuals with an average age of 60 years, 1.7–1.8% sevoflurane has been found to be required.[19,20] These studies used expiratory sevoflurane concentration to calculate the MAC value. In our study, the expiratory sevoflurane concentration was similar between the groups. Sevoflurane tensions in blood were, however, significantly higher with larger V_T. This makes the P_{ET}sevo–$P_a$sevo difference smaller with larger V_T, suggesting that the $P_a$sevo and, subsequently, the depth of

anesthesia might be underestimated when sevoflurane administration is directed by end-tidal values in patients ventilated with large tidal volumes.

The strength of the study presented lies in our measurement of arterial sevoflurane tensions in a study evaluating the effects of different ventilation strategies. This eliminates the confounding effects of ventilation on the measurement of respiratory concentrations. The limitations are that we did not measure any hemodynamic influences on lung circulation and that no baseline lung function tests were performed. Taken together, this should stimulate further studies.

In conclusion, ventilation with larger tidal volumes with isocapnia accomplished with an added apparatus dead space increases the tension of sevoflurane in arterial blood.

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Paper III

ORIGINAL ARTICLE

Increased apparatus dead space and tidal volume increase blood concentrations of oxygen and sevoflurane in overweight patients: a randomised controlled clinical study

Bruno Enekvist, Mikael Bodelsson and Anders Johansson

Background and objective General anaesthesia impairs respiratory function in overweight patients. We wanted to determine whether increased tidal volume (V_T), with unchanged end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$), affects blood concentrations of oxygen and sevoflurane in overweight patients.

Methods The present study is a prospective, randomised, clinical study. American Society of Anesthesiologists physical status I and II patients with BMI over 25 scheduled for elective surgery of the lower abdomen were randomly assigned to one of two groups with 10 patients in each. One group was ventilated with normal V_T (NV_T) and one group with increased V_T (IV_T) achieved by increasing inspired plateau pressure $0.04\,cmH_2O\,kg^{-1}$ above initial plateau pressure. Extra apparatus dead space was added to maintain $P_{ET}CO_2$ at 4.5 kPa. Respiratory rate was set at $15\,min^{-1}$, and sevoflurane was delivered to the fresh gas by a vaporiser set at 3%. Arterial oxygenation, sevoflurane tensions ($P_a$sevo, $F_i$sevo, P_{ET}sevo), $paCO_2$, $P_{ET}CO_2$, V_t and airway pressure were measured.

Results The two groups of patients were similar with regard to sex, age, weight, height and BMI. Arterial oxygen tension (mean ± SD) was significantly higher in the IV_T group (15 ± 4.3 vs. 10 ± 2.7 kPa after 60 min of anaesthesia, $P < 0.05$). Mean P_{ET}sevo did not differ between the groups, whereas arterial sevoflurane tension (mean ± SD) was significantly higher in the IV_T group (1.74 ± 0.18 vs. 1.43 ± 0.19 kPa after 60 min of anaesthesia, $P < 0.05$).

Conclusion Ventilation with larger tidal volumes with isocapnia maintained with added apparatus dead space increases the tension of oxygen and sevoflurane in arterial blood in overweight patients.

Eur J Anaesthesiol 2011;28:000–000

Keywords: anaesthesia, functional residual capacity, pulmonary gas exchange, sevoflurane

Introduction

Respiratory function and pulmonary gas exchange are regularly impaired during general anaesthesia. Atelectasis appears in around 90% of all patients after induction of anaesthesia and Rothen and coworkers found a linear correlation between atelectasis and shunt.[1–4] Some authors describe a relationship between airway closure and the body constitution under general anaesthesia with mechanical ventilation, that is, the functional residual capacity and respiratory compliance decreases exponentially in the supine position with increased BMI.[4,5] In morbidly obese patients, general anaesthesia and paralysis lead to even more atelectasis and an increased risk of hypoxaemia.[6]

Luttropp and Johansson[7] demonstrated a method to ventilate with larger tidal volumes during general anaesthesia with maintained isocapnia by introducing increased apparatus dead space for partial rebreathing of CO_2. In previous studies, we found moderately improved oxygenation and a reduced difference between arterial and exhaled carbon dioxide tension with larger tidal volumes achieved this way in patients with BMI less than $25\,kg\,m^{-2}$.[8] The results were similar to what could be expected from an increase in functional residual capacity (FRC) and also included a more efficient uptake of sevoflurane.[9] We hypothesised that larger tidal volumes would increase arterial concentration of oxygen and volatile anaesthetics in overweight patients as well. In the present study therefore, we determined whether larger tidal volumes affect arterial concentration of oxygen and sevoflurane in patients with BMI over $25\,kg\,m^{-2}$ undergoing abdominal surgery.

Method

Ethics

Ethical approval for this study according to the standards set in the Helsinki declaration (Regional Ethics Committee, Dnr: 480/2007) was provided by Regional Ethics Committee, Lund, Sweden (Chairperson L. Noltorp) on 6 November 2007. Consent to participate in the study was received from each patient.

Patients

The investigation included 20 patients, with the American Society of Anesthesiologists (ASA) physical status 1 or 2, scheduled for elective colon surgery at Skane University Hospital, Lund, Sweden, between September 2009 and January 2010. Patients were considered for inclusion in the trial if they were over 18 years of age and had a BMI more than $25\,kg\,m^{-2}$. All procedures were estimated to last more than 60 min. Patients with known

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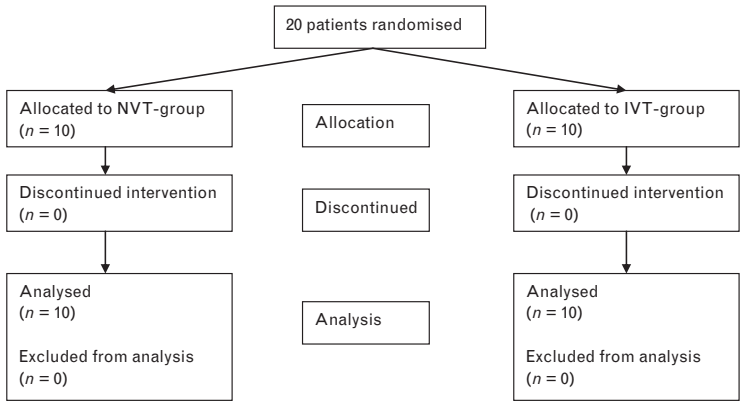
DOI:10.1097/EJA.0b013e328344b4b2

Fig. 1



Patient flow of the study. IVT, Increased tidal volume; NVT, normal tidal volume.

pulmonary or cardiovascular disease were excluded. Patients were randomised to one of two groups with 10 patients in each group via randomly mixed sealed envelope assignment at the start of the procedure in the operating theatre (Fig. 1).

Experimental procedure

Before the start of anaesthesia, an unused carbon dioxide absorber was applied (Drägersorb; Dräger Medical, Lübeck, Germany) to the anaesthesia ventilator (Dräger Primus; Dräger Medical). All patients were preoxygenated with 100% oxygen for 3–4 min with a fresh gas flow of 5 l min^{-1}. Anaesthesia was induced with 2 μg kg^{-1} fentanyl and 1.5–3.0 mg kg^{-1} propofol. Atracurium 0.6 mg kg^{-1} was administered for muscle paralysis. Ventilation was assisted manually with 100% oxygen via a semiopen circle system (4.5 l volume) until tracheal intubation and then by means of ventilator with a FiO_2 at 0.35 in nitrogen. No positive end-expiratory pressure (PEEP) was applied. Propofol 8 mg kg^{-1} h^{-1} was infused until an arterial cannula had been inserted in the radial artery.

In the group with normal tidal volume (NV_T), respiratory rate was set to 15 min^{-1} and V_T was adjusted as to achieve a $P_{ET}CO_2$ at 4.5 kPa. In the group with increased tidal volume (IV_T), respiratory rate was set to 15 min^{-1}. Initial plateau pressure ($P_{plateau}$) was monitored and then V_T was increased until $P_{plateau}$ was 0.04 cmH_2O kg^{-1} over the initial $P_{plateau}$. In a previous study, an increase in $P_{plateau}$ of 0.04 cmH_2O kg^{-1} was found to result in a mean increase in tidal volume of 3.3 ml kg^{-1} in adult patients.[7] The $P_{ET}CO_2$ was then adjusted to 4.5 kPa with a flexible corrugated hose (disposable plastic tube; Medcore AB Uppsala, Sweden) placed between the Y-piece of the anaesthesia circle system and the heat and moisture exchange (HME) filter attached to the endotracheal tube.[7] This flexible corrugated hose increased the dead space volume and provided adjustable rebreathing of carbon dioxide. In both groups, inspiratory : expiratory ratio was 1 : 2, including an inspiratory plateau of 10%. When stable $P_{ET}CO_2$ values reached 4.5 kPa, a control (time zero) sample of arterial blood was obtained and sevoflurane administration was started with a vaporiser (sevoflurane Dräger Vapor 2000; Medical, Lübeck, Germany) set to 3%. After 5 min, the fresh gas flow was adjusted to 1.0 l min^{-1} with an unchanged vaporiser setting throughout the anaesthesia period.

Blood samples of 3 ml were drawn from the arterial line into heparinised syringes at 0, 1, 3, 5, 10, 15, 30, 45 and 60 min after the start of sevoflurane administration (totally 27 ml). Arterial oxygen tension (paO_2), oxygen saturation (S_aO_2) and carbon dioxide tension ($paCO_2$) were analysed using an automatic blood gas analyser (ABL 725; Radiometer, Copenhagen, Denmark). Sevoflurane concentration was analysed with gas chromatography on a Perkin-Elmer 3920 gas liquid chromatograph, as previously described.[9,10]

Patients were monitored with three-lead ECG, heart rate, oxygen saturation, as measured by pulse oximeter (SpO_2), invasive arterial blood pressure via the arterial cannula, (Intelli Vue MP70 Anesthesia; Philips Medizin System, Boeblingen Germany), inspiratory and expiratory oxygen partial pressure (F_iO_2, $P_{ET}O_2$), sevoflurane inspiratory and expiratory partial pressure ($F_i$sevo, P_{ET}-sevo) and carbon dioxide inspiratory and expiratory partial pressure (F_iCO_2, $P_{ET}CO_2$) as analysed by the ventilator. Total ventilation per minute, tidal volumes and airway pressures as peak pressure, plateau pressure and mean pressure were measured and documented at the

same intervals. Static compliance of the respiratory system was calculated as tidal volume divided by the inspiratory plateau pressure.

Extra doses of fentanyl (50–100 μg) were given if mean arterial blood pressure (MAP) increased more than 20% above the initial baseline level. Hypotension (MAP < 60 mmHg) was treated with 5–10 mg ephedrine intravenously. All patients received 3–5 ml $kg^{-1} h^{-1}$ of glucose solution 2.5% with sodium (70 mmol l^{-1}), chloride (45 mmol l^{-1}) and acetate (25 mmol l^{-1}) intravenously. Neuromuscular blockade was monitored with a neuromuscular transmission analyser (TOF-Watch; Organon Technology B V., Boxel Netherlands). Additional doses of atracurium were given at the discretion of the anaesthetist.

Statistics

All statistical analyses were performed with SPSS 16.0 for Windows, (SPSS Inc., Chicago, Illinois, USA). An initial power analysis assuming a $P_a$sevo concentration difference at 0.3 kPa with a SD of 0.2 kPa revealed that seven patients in each group would be needed to achieve a power of 0.8 at P less than 0.05. Ten patients in each group were enrolled. Descriptive variables, tidal volumes, airway pressures, S_PO_2 and lung compliance are expressed as median and interquartile range in square brackets and analysed with a non-parametric method according to the Mann–Whitney test. The values of F_iO_2, $P_{ET}O_2$, $F_i$sevo, P_{ET}sevo, $P_a$sevo and $P_{ET}CO_2$ are presented as mean ± SD and the analysis was conducted with an independent two-tailed t-test. For change of values over time, an analysis with a two-way repeated measurement analysis of variance (ANOVA) was used. The ANOVA analysis was followed by Greenhouse–Geisser post-hoc test. A P value less than 0.05 was considered to indicate statistical significance.

Results

The two groups of patients were similar with regard to sex, age, weight, height and BMI (Table 1). No intraoperative problems were noted during the study. All patients recovered from anaesthesia and left the postoperative unit in accordance with the routines assigned for the surgical procedure.

Table 1 Patient data

	NV_T	IV_T
Number of patients	10	10
Women (*n*)	6	5
Age (years)	64 (52–78)	64 (54–68)
Weight (kg)	84 (78–101)	81 (79–85)
Height (m)	1.64 (1.60–1.75)	1.74 (1.65–1.77)
BMI (kg m^{-2})	30 (26–36)	27 (26–28)

Values are median with interquartile range within brackets. The two groups were similar regarding sex, age, weight, height or BMI.

Tidal volumes were significantly larger in the IV_T group (Table 2). Peak and mean airway pressures were also significantly higher in the IV_T group compared to the NV_T group (Table 2). The median adjustable dead space volume between the Y-piece and HME in the IV_T group was 3.0 (2.8–4.0) ml^{-1} kg and lung compliance was higher in the IV_T group throughout the observation period ($P < 0.05$, Table 2).

Mean end-tidal carbon dioxide values ($P_{ET}CO_2$) were similar in the two groups (Table 3). pa_{CO_2} was, however, lower in the IV_T group throughout the observation period ($P < 0.05$, Table 3) and the difference between pa_{CO_2} and $P_{ET}CO_2$ was smaller in the IV_T group compared to the NV_T group ($P < 0.05$, Table 3).

All patients received ventilation with a F_iO_2 of 35%, except three patients from the NV_T group, who received an increased F_iO_2 after a period of S_PO_2 less than 91%. The values of S_PO_2 and pa_{O_2} were significantly higher in the IV_T group compared to the NV_T group ($P < 0.05$, Table 4).

P_{ET}sevo was lower in the IV_T group between 1 and 5 min ($P < 0.05$, Fig. 2), but not between 10 and 60 min (Table 5). Mean $P_a$sevo was higher in the IV_T group compared to the NV_T group from 5 min and the difference increased with time ($P < 0.05$, Table 5, Fig. 2). The difference between $P_a$sevo and P_{ET}sevo was smaller in the IV_T group compared to the NV_T group ($P < 0.05$, Table 5, Fig. 2).

Discussion

In the present study, mean pa_{O_2} and $P_a$sevo were found to be higher in overweight patients ventilated with larger tidal volumes. This is in line with previous results obtained from patients with normal weight.[8,9] Mean F_iO_2 and $F_i$sevo did not differ between the groups. Thus, differences in inspired concentrations could be ruled out as explanations for the increased oxygen and sevoflurane uptake in the IV_T group.

Reduced FRC makes airway closure more frequent, which is a likely explanation for the appearance of regions with a low ventilation/perfusion ratio and atelectasis during anaesthesia.[4,11] In fact, atelectasis and airway closure may explain 75% of the deterioration in pa_{O_2}.[4] Neumann *et al.*[12] demonstrated a significant inverse correlation between pa_{O_2} and atelectasis. In the present study, plateau pressure did not differ between the two groups, but tidal volume was considerably larger in the IV_T group compared with the NV_T group resulting in larger lung compliance in the IV_T group. A plausible explanation for the increase in compliance is recruitment or decreased loss of ventilated lung tissue by the larger tidal volume. This is supported by the findings by Erlandsson *et al.*[13] who showed that a recruitment manoeuvre resulted in decreased plateau pressure and increased lung compliance with a decreased shunt.

Table 2 Comparison of tidal volumes (V_T), tidal volume kg body weight^{-1}, peak, plateau, mean airway pressures and lung compliance in the normal tidal volume group (NV_T) and increased tidal volume group (IV_T)

	5 min	30 min	60 min
V_T (ml)			
NV_T	400 (340–467)	440 (380–478)	397 (362–428)
IV_T	777 (708–812)∗	750 (703–808)∗	717 (692–807)∗
V_T (ml kg^{-1})			
NV_T	4.6 (4.3–5.3)	4.9 (4.5–5.2)	5.0 (4.5–5.1)
IV_T	9.3 (8.6–10)∗	9.2 (8.7–9.7)∗	9.0 (8.7–9.8)∗
P-Peak (cmH_2O)			
NV_T	16.5 (12.0–23.3)	16.0 (13.0–22.3)	15.5 (14.0–22.5)
IV_T	24.5 (21.5–26.5)∗	25.0 (23.0–25.5)∗	25.5 (22.8–27.8)∗
P-Plateau (cmH_2O)			
NV_T	15.0 (11.8–20.3)	14.5 (11.8–17.8)	15.0 (12.8–19.8)
IV_T	18.5 (15.0–20.0)	16.0 (11.8–17.8)	17.5 (15.0–21.5)
P-Mean (cmH_2O)			
NV_T	6.0 (4.0–7.0)	5.0 (4.0–6.3)	4.0 (4.0–6.3)
IV_T	7.0 (6.0–9.0)∗	7.0 (6.0–8.3)∗	7.0 (6.8–9.0)∗
Lung compliance (ml cmH_2O^{-1})			
NV_T	28 (23–34)	29 (21–33)	27 (21–31)
IV_T	41 (37–53)∗	48 (36–58)∗	41 (31–52)∗

Values are median (interquartile range), $n = 10$ in each group. P-Plateau values were not statistically significantly different between the two groups. The values of V_T (ml), V_T (ml kg^{-1}), P-Peak, P-Mean and lung compliance were statistically significantly larger in the IV_T group compared to the NV_T group Mann–Whitney test (∗, $=P < 0.05$).

It is reasonable to assume that the recruitment of ventilated lung tissue increased FRC in the IV_T group. This is in line with the results presented by Reinius *et al.*[14] who showed that a recruitment manoeuvre followed by PEEP reduced atelectasis, improved oxygenation and increased compliance in obese patients. Conversely, the lower value of lung compliance in the NV_T group could indicate more atelectasis of lung tissue in this group. This is supported by the need to increase F_iO_2 in three patients of this group in order to maintain a SpO_2 above 90%, indicating pulmonary shunting of venous blood. Pelosi *et al.*[5] found that an increase in BMI can be related to a reduction in FRC after induction of anaesthesia,

Table 3 Comparison of the values for the expiratory carbon dioxide ($P_{ET}CO_2$), carbon dioxide pressures in arterial blood ($paco_2$) and $paco_2$–$P_{ET}CO_2$ difference (P_a–$P_{ET}CO_2$) between normal tidal volume group (NV_T) and increased tidal volume group (IV_T)

	5 min	30 min	60 min
$P_{ET}CO_2$ (kPa)			
NV_T	4.3 ± 0.28	4.4 ± 0.27	4.4 ± 0.22
IV_T	4.6 ± 0.32	4.6 ± 0.33	4.5 ± 0.07
$paco_2$ (kPa)			
NV_T	5.2 ± 0.36	5.5 ± 0.25	5.5 ± 0.31
IV_T	5.0 ± 0.32∗	5.2 ± 0.36∗	5.0 ± 0.20∗
P_a–$P_{ET}CO_2$ (kPa)			
NV_T	0.92 ± 0.32	1.1 ± 0.21	1.1 ± 0.30
IV_T	0.42 ± 0.22∗	0.57 ± 0.36∗	0.53 ± 0.21∗

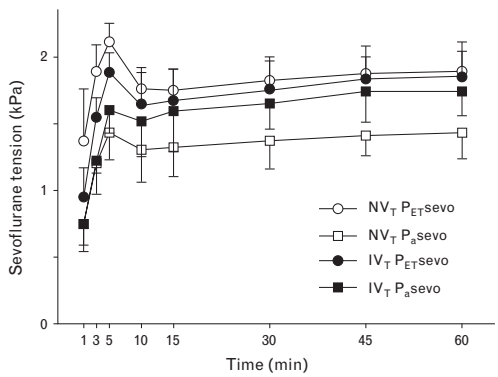
Values are mean ± SD ($n = 10$ in each group). $P_{ET}CO_2$ values were similar in the two groups. The values of $paco_2$ and P_a–$P_{ET}CO_2$ were statistically significantly lower in the IV_T group compared to the NV_T group. Independent two-tailed *t*-test (∗, $P < 0.05$).

Table 4 Comparison of the values for the inspiratory oxygen concentrations (F_iO_2), oxygen saturation, as measured by pulse oximeter (S_PO_2), and oxygen tension (paO_2), between normal tidal volume group (NV_T) and increased tidal volume group (IV_T)

	5 min	30 min	60 min
F_iO_2 (%)			
NV_T	35 ± 2.1	37 ± 2.3	37 ± 5.5
IV_T	35 ± 1.0	35 ± 1.0	35 ± 0.5
S_PO_2 (%)			
NV_T	96 (92–98)	96 (93–97)	94 (91–98)
IV_T	100 (99–100)∗	100 (99–100)∗	99 (98–100)∗
paO_2 (kPa)			
NV_T	11 ± 3.8	11 ± 2.9	10 ± 2.7
IV_T	16 ± 3.0∗	17 ± 3.8∗	15 ± 4.3∗

Values of S_PO_2 are median (interquartile range) and values of F_iO_2 and paO_2 are mean ± SD ($n = 10$ in each group). F_iO_2 values were similar in the two groups. S_PO_2 and paO_2 were statistically significantly higher in the IV_T group compared to the NV_T group. Mann–Whitney test and independent two-tailed *t*-test, respectively, (∗, $P < 0.05$).

Fig. 2



Comparison of the values for arterial sevoflurane ($P_a$sevo) and end-tidal sevoflurane tension (P_{ET}sevo) between the increased tidal volume group (IV_T) and normal tidal volume group (NV_T). Values are mean ± SD ($n = 10$ in each group). The expiratory sevoflurane concentration was similar in the two groups except before and at 5 min when it was statistically significantly lower in the IV_T group. Arterial sevoflurane tensions were statistically significantly higher in the IV_T group compared to the NV_T group and the differences increased with time. Two-way repeated measurement analysis of variance (ANOVA) followed by Greenhouse–Geisser post-hoc test ($P < 0.05$).

Table 5 Comparison of the values for the inspiratory sevoflurane concentrations ($F_i$sevo), expiratory sevoflurane concentrations (P_{ET}sevo), arterial sevoflurane tensions ($P_a$sevo) and P_{ET}sevo−$P_a$sevo difference (P_{ET}−$P_a$sevo) between normal tidal volume group (NV_T) and increased tidal volume group (IV_T)

	5 min	30 min	60 min
$F_i$sevo (kPa)			
NV_T	2.80 ± 0.28	2.24 ± 0.20	2.30 ± 0.24
IV_T	2.64 ± 0.19	2.18 ± 0.20	2.24 ± 0.17
P_{ET}sevo (kPa)			
NV_T	2.10 ± 0.15	1.82 ± 0.18	1.89 ± 0.22
IV_T	1.88 ± 0.15*	1.76 ± 0.21	1.85 ± 0.19
$P_a$sevo (kPa)			
NV_T	1.43 ± 0.20	1.37 ± 0.21	1.43 ± 0.19
IV_T	1.60 ± 0.17*	1.65 ± 0.19*	1.74 ± 0.18*
P_{ET}−$P_a$sevo (kPa)			
NV_T	0.68 ± 0.29	0.46 ± 0.19	0.46 ± 0.23
IV_T	0.28 ± 0.17*	0.11 ± 0.12*	0.11 ± 0.13*

Values of $F_i$sevo, P_{ET}sevo, $P_a$sevo and P_{ET}−$P_a$sevo are mean ± SD ($n = 10$ in each group). $F_i$sevo and P_{ET}sevo values were not significantly different between the groups except P_{ET}sevo, which was statistically significantly lower in the IV_T group before and at 5 min. Arterial sevoflurane tensions were statistically significantly higher in the IV_T group compared to the NV_T group. P_{ET}sevo−$P_a$sevo differences were statistically significantly lower in the IV_T group compared to the NV_T group. Two-way repeated measurement analysis of variance (ANOVA) followed by Greenhouse-Geisser post-hoc test (*, $P < 0.05$).

which makes atelectasis more frequent. It should be noted that we did not directly assess the development of atelectasis in the present study. Thus, apart from reduced atelectasis our findings could at least partly be explained by increased alveolar ventilation in the IV_T group.

Patients in the NV_T group received an average tidal volume of 5.0 ml kg^{-1} (total weight), and probably develop regions of abnormal ventilation/perfusion. Routinely, PEEP of 5–10 cmH_2O is applied in order to prevent this. The present results suggest that increasing tidal volumes might have a similar effect. However, a possible intrinsic PEEP could have influenced the oxygenation and arterial sevoflurane concentrations in our patients. Unfortunately, our equipment did not measure intrinsic PEEP levels, which is a limitation of the study. A randomised study comparing PEEP with large tidal volumes during anaesthesia in overweight patients is, therefore, needed to test this hypothesis.

The $paCO_2$ levels were slightly lower in the IV_T group and could contribute to increased $P_a$sevo levels by means of increased ventilation alone. However, the $P_{ET}CO_2$ levels were similar between the groups and indicate that the increased levels of $P_a$sevo could be explained by increased alveolar ventilation in the IV_T group. The P_{ET}sevo − $P_a$sevo difference was greater in the group ventilated with smaller tidal volumes in the absence of PEEP. This must be kept in mind in order to avoid overestimation of depth of anaesthesia when assessing on the basis of P_{ET}sevo in patients ventilated this way.

In conclusion, in patients with BMI over 25 kg m^{-2}, ventilation with larger tidal volumes with isocapnia accomplished with an added apparatus dead space improves oxygen and sevoflurane uptake in arterial blood.

Acknowledgement

The funding for the present study was restricted to institutional and department sources and there were no conflicts of interest.

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